Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Total Synthesis of Thioamycolamide A Using Diastereoselective Sulfa-Michael Addition as the Key Step

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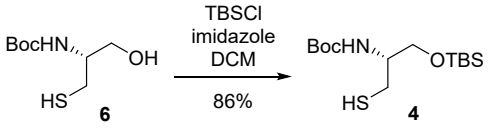
I. General Information

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen or argon. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions in *vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. All reaction solvents were purified before use: Tetrahydrofuran was distilled from sodium; toluene was distilled over molten sodium metal; dichloromethane, dimethylformamide, diethylamine, triethylamine and diisopropylethylamine were distilled from CaH_2; and methanol was distilled from Mg/I_2. Flash column chromatography was performed using the corresponding solvents on E. Qingdao silica gel 60 (230 – 400 mesh ASTM). TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm). Compounds were visualized with UV light, iodine, *p*-anisaldehyde stain, ceric ammonium molybdate stain, or phosphomolybdic acid in EtOH. ^{1}H NMR spectra were recorded on Bruker Avance 300 MHz, Avance 400 MHz or Avance 500 MHz spectrometers. Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals of the solvent. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets; other combinations are derived from those listed above. Coupling constants (*J*) are reported in Hertz (Hz) for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δH (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 75 MHz, a 101 MHz or a 126 MHz spectrometer for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δC (77.16 ppm) and DMSO-d_6 δC (39.52 ppm). High resolution mass spectra were measured on ABI Q-star Elite. Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Optical rotations were recorded on a Rudolph AutoPol-I polarimeter at 589 nm, 50 mm cell. Data were reported as follow: optical rotation (*c* (g/100 mL), solvent).

II. Experimental Details and Spectral Data

tert-butyl (*R*)-(1-((*tert*-butyldimethylsilyl)oxy)-3-mercaptopropan-2-yl)carbamate



To a solution of **6** (1.2 g, 5.9 mmol, 1.0 equiv.) in anhydrous DCM (20 mL, 0.3 M) were added imidazole (1.0 g, 14.2 mmol, 2.4 equiv.) and TBSCl (1.1 g, 7.1 mmol, 1.2 equiv.) at 0 °C, and the resulting mixture was stirred at ambient temperature for 3 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (EtOAc/Hexanes = 1/50) to furnish **4** in 86% yield (1.6 g, 5.0 mmol) as a colorless oil.

R_f = 0.40 (Hexanes:EtOAc = 50:1), PMA stain.

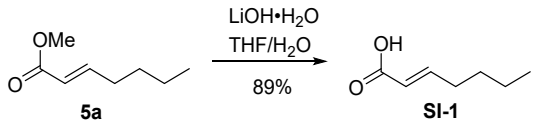
$[\alpha]_D^{28}$ = -1.9 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, CD_3OD): δ 6.31 (d, *J* = 7.7 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.68 – 3.59 (m, 2H), 2.71 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.62 (dd, *J* = 13.6, 6.2 Hz, 1H), 1.47 (s, 9H), 0.93 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (101 MHz, CD_3OD) δ 156.6, 79.0, 63.1, 54.7, 27.7, 25.3, 18.0, -6.2.

HRMS (ESI, *m/z*) for $C_{14}H_{31}NO_3SSiNa^+$ $[M+Na]^+$: Calcd. 344.1686; Found 344.1692.

(*E*)-hept-2-enoic acid



To a solution of **5a** (3.8 g, 27 mmol, 1.0 equiv.) in a 1:1 mixture of THF:H_2O (90 mL, 0.30 M) at 0 ºC, LiOH·H_2O (5.7 g, 135 mmol, 5.0 equiv.) was added. After being stirred for 12 h at room temperature, the solvents were removed *in vacuo*. The residue was diluted with water (150 mL), acidified to pH=2 with HCl (1.0 M in water), and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired acid **SI-1** in 89% yield (3.0 g, 24 mmol) as a colorless oil.

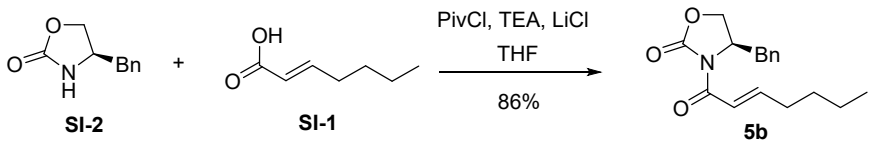
R_f = 0.60 (Hexanes:EtOAc = 4:1), PMA stain.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (dt, *J* = 15.4, 1.7 Hz, 1H), 2.31 – 2.17 (m, 2H), 1.51 – 1.41 (m, 2H), 1.40 – 1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 152.5, 120.7, 32.0, 29.9, 22.2, 13.7.

HRMS (ESI, *m/z*) for $C_7H_{13}O_2^+$ $[M + H]^+$: Calcd. 129.0910; Found 129.0912.

(*R*,*E*)-4-benzyl-3-(hept-2-enoyl)oxazolidin-2-one



To a solution of **SI-1** (160 mg, 1.2 mmol, 1.0 equiv.) in THF (10 mL, 0.12 M) was added TEA (0.43 mL, 3.1 mmol, 2.5 equiv.) and trimethylacetyl chloride (0.15 mL, 1.2 mmol, 1.0 equiv.) at -20 °C. The reaction mixture was stirred for 1 h at -20 °C, and then **SI-2** (211 mg, 1.2 mmol, 1.0 equiv.) dissolved in THF (2 mL) was added via syringe. After being stirred at -20 °C for 1 h, it was slowly warmed to ambient temperature and stirred for 1 h and then quenched with saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) to furnish **5b** in 86% yield (308 mg, 1.1 mmol) as a white solid.

R_f = 0.60 (Hexanes:EtOAc = 4:1), UV & PMA stain.

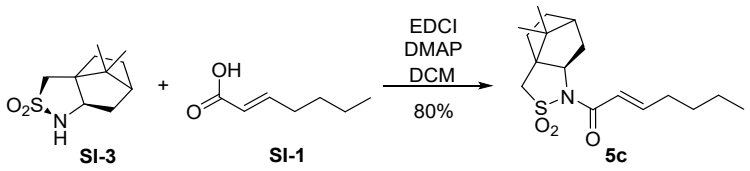
$[\alpha]_D^{28}$ = -33.3 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.30 – 7.20 (m, 5H), 4.84 – 4.61 (m, 1H), 4.30 – 4.08 (m, 2H), 3.33 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.81 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.32 (td, *J* = 7.4, 5.6 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.39 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 153.6, 152.0, 135.6, 129.6, 129.1, 127.4, 120.5, 66.2, 55.4, 38.0, 32.5, 30.3, 22.43, 14.0.

HRMS (ESI, *m/z*) for $C_{17}H_{22}NO_3^+$ $[M+H]^+$: Calcd. 288.1594; Found 288.1596.

(*E*)-1-((7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)hept-2-en-1-one



To a solution of **SI-3** (252 mg, 1.2 mmol, 1.0 equiv.) and **SI-1** (150 mg, 1.2 mmol, 1.0 equiv.) in DCM (4.0 mL, 0.30 M) at 0 °C was added EDCI (450 mg, 2.3 mmol, 2.0 equiv.), followed by addition of DMAP (142 mg, 1.2 mmol, 1.0 equiv.). The reaction mixture was slowly warmed to ambient temperature and stirred for 9 h before being quenched with saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **5c** in 80% yield (304 mg, 0.94 mmol) as a white solid.

R_f = 0.20 (Hexanes:EtOAc = 9:1), UV & PMA stain.

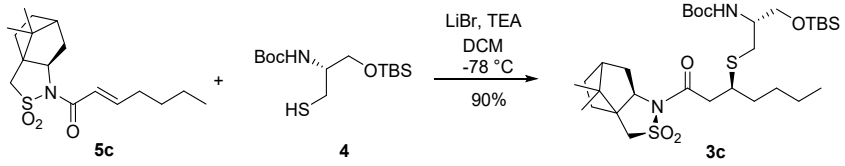
$[\alpha]_D^{28}$ = -44.3 (c 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dt, J = 15.1, 7.0 Hz, 1H), 6.55 (dt, J = 15.1, 1.6 Hz, 1H), 3.93 (dd, J = 7.6, 5.1 Hz, 1H), 3.48 (q, J = 13.8 Hz, 2H), 2.32 – 2.22 (m, 2H), 2.19 – 2.06 (m, 2H), 1.99 – 1.82 (m, 3H), 1.52 – 1.38 (m, 3H), 1.40 – 1.30 (m, 3H), 1.18 (s, 3H), 0.98 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 151.1, 120.9, 65.3, 53.3, 48.5, 47.9, 44.8, 38.7, 33.0, 32.3, 30.2, 26.6, 22.4, 21.0, 20.0, 13.9.

HRMS (ESI, *m/z*) for $C_{17}H_{27}NO_3SNa^+$ $[M+Na]^+$: Calcd. 348.1604; Found 348.1607.

***tert*-butyl ((2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-(((2*S*)-1-((7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-1-oxoheptan-2-yl)thio)propan-2-yl)carbamate**



An oven-dried round-bottom flask was charged with **5c** (1.0 g, 3.2 mmol, 1.0 equiv.) and LiBr (278 mg, 3.2 mmol, 1.0 equiv.), and anhydrous DCM (50 mL, 0.065 M) was added under argon atmosphere. The

reaction mixture was stirred for 0.5 h at -78 °C before TEA (0.44 mL, 3.2 mmol, 1.0 equiv.) and **4** (1.5 g, 4.8 mmol, 1.5 equiv.) were added. The reaction mixture was further stirred at -78 °C for 9 h before being quenched with saturated aqueous solution of NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **3c** in 90% yield (1.9 g, 2.9 mmol) as a colorless oil.

R_f = 0.20 (Hexanes:EtOAc = 9:1), UV & PMA stain.

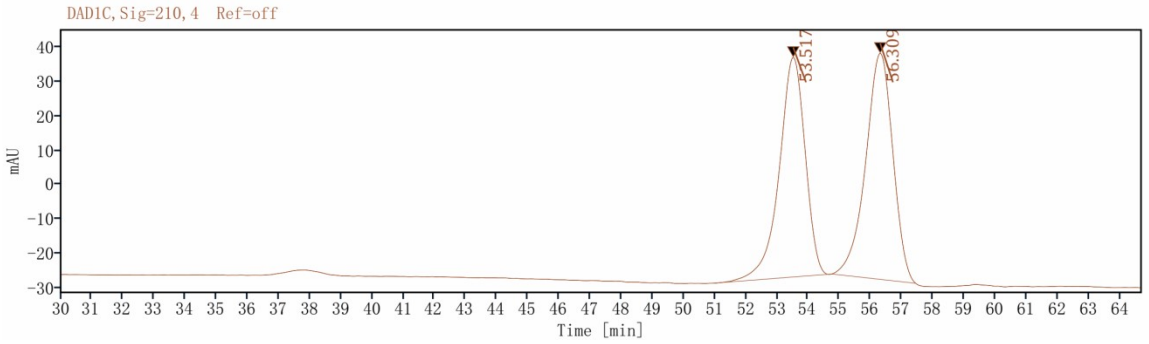
$[\alpha]_D^{26}$ = -19.6 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, *J* = 8.4 Hz, 1H), 3.84 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.74 (d, *J* = 9.5 Hz, 2H), 3.57 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.50 – 3.38 (m, 2H), 3.17 (q, *J* = 7.0 Hz, 1H), 3.01 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.77 (dd, *J* = 16.1, 5.7 Hz, 1H), 2.65 (d, *J* = 8.8 Hz, 2H), 2.17 – 1.96 (m, 2H), 1.92 – 1.80 (m, 3H), 1.58 (ddd, *J* = 9.6, 6.4, 3.2 Hz, 2H), 1.41 (s, 9H), 1.38 – 1.21 (m, 6H), 1.15 (s, 3H), 0.94 (s, 3H), 0.88 – 0.82 (m, 12H), 0.01 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 155.1, 79.1, 65.1, 62.9, 53.0, 51.2, 48.4, 47.7, 44.7, 42.1, 41.4, 38.4, 35.0, 32.8, 31.7, 28.8, 28.4, 26.4, 25.9, 22.5, 20.8, 19.9, 18.2, 14.0, -5.4, -5.4.

HRMS (ESI, *m/z*) for $C_{31}H_{58}N_2O_6S_2SiNa^+$ $[M+Na]^+$: Calcd. 669.3398; Found 669.3403.

HPLC (100-5-C18 columns, MeCN:H_2O = 92:8, 2.0 mL/min, 210 nm), d.r. = 95:5.



Signal: DAD1C, Sig=210, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
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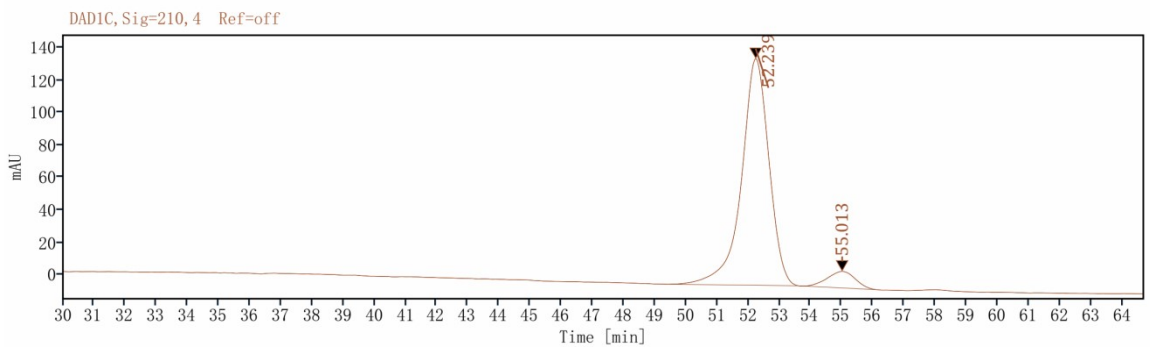
56.309	0.91	3977.99	65.53	51.89
	Totals	7665.97		



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52.239	0.91	8467.23	139.30	94.86
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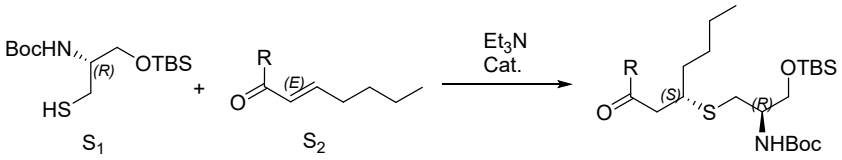
	Totals	8925.70		

Table I. Pivotal sulfa-Michael addition reaction.[a]

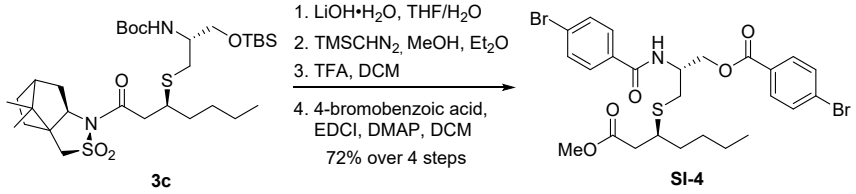


Entry	R	Solvent	Lewis acid	Base	Temp. (°C)	% conv. (d.r.)[b]
1	OMe	CH_2Cl_2	NA	0.1eq Et_3N	r.t.	0 (---)
2	Evans	CH_2Cl_2	NA	0.1eq Et_3N	r.t.	54 (1.1:1)
3	Oppolzer	CH_2Cl_2	NA	0.1eq Et_3N	r.t.	54 (1.4:1)
4	Oppolzer	CH_2Cl_2	NA	1eq Et_3N	r.t.	70 (1.5:1)
6	Oppolzer	CH_2Cl_2	NA	2eq Et_3N	r.t.	71 (1.5:1)
7	Oppolzer	CH_2Cl_2	$CuCl_2$	1eq Et_3N	r.t.	0 (---)
8	Oppolzer	CH_2Cl_2	$ZnBr_2$	1eq Et_3N	r.t.	0 (---)
9	Oppolzer	CH_2Cl_2	$MgCl_2$	1eq Et_3N	r.t.	0 (---)
10	Oppolzer	CH_2Cl_2	$TiCl_4$	1eq Et_3N	r.t.	0 (---)
11	Oppolzer	CH_2Cl_2	LiBr	1eq Et_3N	r.t.	84 (4:1)

12	Oppolzer	THF	LiBr	1eq Et_3N	r.t.	51 (1.4:1)
13	Oppolzer	PhMe	LiBr	1eq Et_3N	r.t.	59 (3.3:1)
14	Oppolzer	MeCN	LiBr	1eq Et_3N	r.t.	80 (2.5:1)
15	Oppolzer	MeOH	LiBr	1eq Et_3N	r.t.	50 (1:1)
16	Oppolzer	Et_2O	LiBr	1eq Et_3N	r.t.	41 (2.5:1)
17	Oppolzer	CH_2Cl_2	LiBr	1eq Et_3N	0	83 (5.2:1)
18[c]	Oppolzer	CH_2Cl_2	LiBr	1eq Et_3N	-78	90 (19:1)[d]

[a] Reaction conditions: **S_1** (1.5 equiv.), **S_2** (1.0 equiv.), and Lewis acid (1.0 equiv.) were dissolved in solvent (0.1 M), followed by the addition of Et_3N (0.1 or 1.0 equiv.), and stirred for 6-9 h, unless stated otherwise; [b] The ratio of diastereomeric products was determined d by ^1H NMR analysis with an internal standard; [c] **S_2** (1.0 equiv.), and Lewis acid (1.0 equiv.) were premixed for 30 min before the addition of **S_1** (1.5 equiv.) and Et_3N (1.0 equiv.); [d] Isolated yield, and the ratio of diastereomeric products was determined by HPLC.

(*R*)-2-(4-bromobenzamido)-3-(((*S*)-1-methoxy-1-oxoheptan-3-yl)thio)propyl 4-bromobenzoate



To a solution of **3c** (265 mg, 0.27 mmol, 1.0 equiv.) in 10 mL (0.30 M) of a 1:1 mixture of THF:H_2O, LiOH·H_2O (113 mg, 2.7 mmol, 10 equiv.) was added at 0 °C. After being stirred for 9 h at room temperature, the solvents were removed in *vacuo*, and the residue was diluted with water (5 mL), and DCM (10 mL) was added followed by slow addition of NaOH (1N) until the pH of the aqueous phase was ~ 11, and the Oppolzer's sultam was recovered from the DCM layer. The aqueous layer was then acidified to pH=2 with HCl (1.0 M in water), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired acid as a colorless oil, which was used directly in the next step without further purification.

To a solution of the crude acid generated above in 10 mL of a 4:1mixture of Et_2O:MeOH, $TMSCHN_2$ (0.20 mL) was added at 0 °C. After being stirred for 1 h at room temperature, the *in situ* produced methyl ester was concentrated in *vacuo* and used directly in the next step without further purification.

To a solution of above methyl ester in DCM (3 mL) was added TFA (3 mL) dropwise at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was concentrated. Toluene (1 mL) was added and the solution was concentrated (x 3, to remove trifluoroacetic acid) to afford the crude amino ester, which was used directly in the next step without further purification.

To a solution of above amino ester and 4-bromobenzoic acid (108 mg, 0.54 mmol, 2.0 equiv.) in DCM (6.0 mL, 0.050 M) at 0 °C was added EDCI (259 mg, 1.4 mmol, 5.0 equiv.), followed by addition of DMAP (99 mg, 0.81 mmol, 3.0 equiv.). The reaction mixture was slowed warmed to ambient temperature and stirred for 9 h, then quenched with saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) providing 110 mg (0,19 mmol) of the corresponding amide **SI-4** in 72% yield (for four steps) as a colorless oil.

R_f = 0.60 (Hexanes:EtOAc = 4:1), UV & PMA stain.

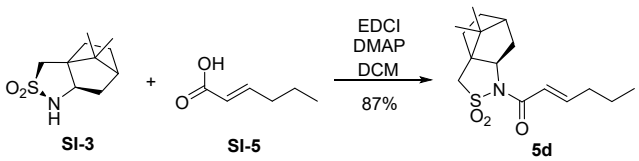
$[\alpha]_D^{26}$ = -14.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, CD_3OD):δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.65 (t, *J* = 8.8 Hz, 4H), 4.69 – 4.61 (m, 1H), 4.58 (dd, *J* = 11.9, 3.5 Hz, 1H), 4.47 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.67 (s, 3H), 3.21 – 3.11 (m, 1H), 2.99 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.87 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.72 – 2.56 (m, 2H), 1.72 – 1.52 (m, 2H), 1.52 – 1.38 (m, 2H), 1.36 – 1.24 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ 173.8, 169.4, 167.0, 134.8, 133.0, 132.8, 132.4, 130.3, 129.2, 127.2, 66.7, 52.2, 50.5, 43.3, 41.7, 36.0, 32.4, 30.2, 23.5, 14.3.

HRMS (ESI, *m/z*) for $C_{25}H_{30}Br_2NO_5S^+$ $[M + H]^+$: Calcd. 614.0206; Found 614.0202.

(*E*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)hex-2-en-1-one



To a solution of **SI-3** (1.1 g, 5.3 mmol, 1.0 equiv.) and **SI-5** (0.60 g, 5.3 mmol, 1.0 equiv.) in DCM (18 mL, 0.30 M) was added EDCI (2.0 g, 11 mmol, 2.0 equiv.) at 0 °C, followed by addition of DMAP (118

mg, 1.1 mmol, 0.20 equiv.). The reaction mixture was slowly warmed to ambient temperature and stirred for 9 h before it was quenched with saturated aqueous solution of NH_4Cl (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **5d** in 87% yield (1.4 g, 4.6 mmol) as a white solid.

R_f = 0.30 (Hexanes:EtOAc = 9:1), UV & PMA stain.

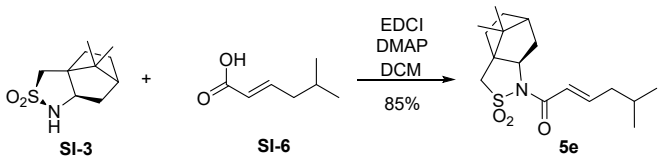
$[\alpha]_D^{28}$ = -92.4 (c 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (dt, J = 14.7, 7.0 Hz, 1H), 6.54 (d, J = 15.0 Hz, 1H), 3.91 (dd, J = 7.7, 4.9 Hz, 1H), 3.55 – 3.36 (m, 2H), 2.22 (q, J = 7.3 Hz, 2H), 2.17 – 2.00 (m, 2H), 1.95 – 1.81 (m, 3H), 1.49 (q, J = 7.4 Hz, 2H), 1.45 – 1.38 (m, 1H), 1.39 – 1.30 (m, 1H), 1.16 (s, 3H), 0.96 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.2, 150.8, 121.0, 65.2, 53.2, 48.5, 47.8, 44.7, 38.5, 34.5, 32.9, 26.5, 21.3, 20.9, 19.9, 13.7.

HRMS (ESI, *m/z*) for $C_{16}H_{25}NO_3SNa^+$ $[M+Na]^+$: Calcd. 334.1147; Found 334.1147.

(*E*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-5-methylhex-2-en-1-one



To a solution of **SI-3** (1.0 g, 4.7 mmol, 1.0 equiv.) and **SI-6** (0.61 g, 4.7 mmol, 1.0 equiv.) in DCM (16 mL, 0.30 M) was added EDCI (1.8 g, 9.5 mmol, 2.0 equiv.) at 0 °C, followed by addition of DMAP (106 mg, 0.95 mmol, 0.20 equiv.). The reaction mixture was slowly warmed to ambient temperature and stirred for 9 h before it was quenched with saturated aqueous solution of NH_4Cl (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **5e** in 85% yield (1.3 g, 4.0 mmol) as a white solid.

R_f = 0.40 (Hexanes:EtOAc = 9:1), UV & PMA stain.

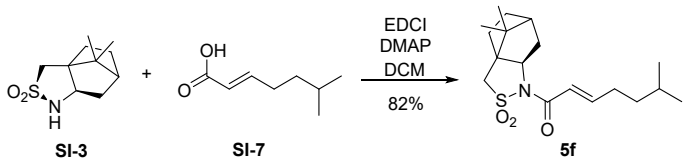
$[\alpha]_D^{28}$ = -106.2 (*c* 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (dt, *J* = 15.0, 7.5 Hz, 1H), 6.54 (dt, *J* = 15.1, 1.4 Hz, 1H), 3.93 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.61 – 3.33 (m, 2H), 2.19 – 2.04 (m, 4H), 1.95 – 1.84 (m, 3H), 1.85 – 1.70 (m, 1H), 1.45 – 1.32 (m, 2H), 1.18 (s, 3H), 0.97 (s, 3H), 0.93 (dd, *J* = 6.7, 1.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.2, 149.8, 121.9, 65.2, 53.2, 48.5, 47.8, 44.8, 41.7, 38.6, 32.9, 27.9, 26.5, 22.4, 22.4, 20.9, 19.9.

HRMS (ESI, *m/z*) for $C_{17}H_{27}NO_3SNa^+$ $[M+Na]^+$: Calcd. 348.1604; Found 348.1604.

(*E*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-6-methylhept-2-en-1-one



To a solution of **SI-3** (538 mg, 2.5 mmol, 1.0 equiv.) and **SI-7** (426 mg, 3.0 mmol, 1.2 equiv.) in DCM (10 mL, 0.25 M) was added EDCI (960 mg, 5.0 mmol, 2.0 equiv.) at 0 °C, followed by addition of DMAP (305 mg, 2.5 mmol, 1.0 equiv.). The reaction mixture was slowly warmed to ambient temperature and stirred for 9 h before it was quenched with saturated aqueous solution of NH_4Cl (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **5f** in 82% yield (695 mg, 2.1 mmol) as a white solid.

R_f = 0.60 (Hexanes:EtOAc = 4:1), UV & PMA stain.

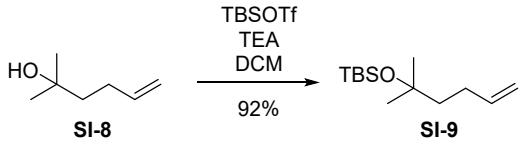
$[\alpha]_D^{28}$ = -49.2 (*c* 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.46 (dt, *J* = 15.2, 1.6 Hz, 1H), 3.83 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.50 – 3.32 (m, 2H), 2.21 – 2.12 (m, 2H), 2.08 – 1.94 (m, 2H), 1.87 – 1.73 (m, 3H), 1.58 – 1.43 (m, 1H), 1.38 – 1.31 (m, 1H), 1.29 – 1.22 (m, 3H), 1.08 (s, 3H), 0.89 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.0, 150.8, 120.7, 65.0, 53.1, 48.4, 47.7, 44.7, 38.5, 36.9, 32.7, 30.4, 27.6, 26.5, 22.4, 22.3, 20.8, 19.9.

HRMS (ESI, *m/z*) for $C_{18}H_{29}NO_3SNa^+$ [M+Na]$^+$: Calcd. 362.1760; Found 362.1760.

***tert*-butyldimethyl((2-methylhex-5-en-2-yl)oxy)silane**



To a solution of **SI-8** (1.9 g, 17 mmol, 1.0 equiv.) in anhydrous DCM (40 mL, 0.40 M) were added TEA (12 mL, 14 mmol, 5.0 equiv.) and TBSOTf (12 mL, 51 mmol, 3.0 equiv.) at 0 °C. The resulting mixture was stirred at ambient temperature for 3 h, before it was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (EtOAc/Hexanes = 1/100) to furnish **SI-9** in 92% yield (3.7 g, 16 mmol) as a colorless oil.

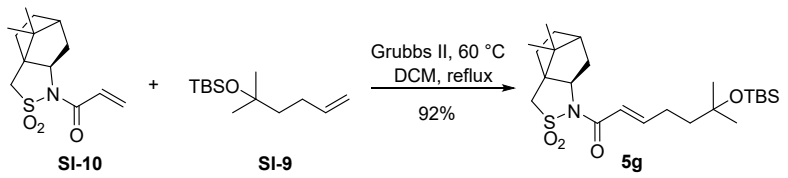
R_f = 0.80 (Hexanes:EtOAc = 100:1), PMA stain.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.07 – 4.90 (m, 2H), 2.21 – 2.10 (m, 2H), 1.58 – 1.44 (m, 2H), 1.23 (s, 6H), 0.89 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.6, 113.8, 73.2, 44.2, 29.8, 28.8, 25.9, 25.7, 18.1, -2.1, -2.9.

HRMS (ESI, *m/z*) for $C_{13}H_{28}OSiNa^+$ [M+Na]$^+$: Calcd. 251.1802; Found 251.1804.

(*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-6-methylhept-2-en-1-one



To a solution of **SI-10** (0.60 g, 2.2 mmol, 1.0 equiv.) and **SI-9** (1.0 g, 4.5 mmol, 2.0 equiv.) in DCM (10 mL, 0.25 M) was added Grubbs II catalyst (94 mg, 0.11 mmol, 0.050 equiv.). The reaction mixture was heated to reflux and stirred for 9 h before it was concentrated under reduced pressure. The residue was

subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **5g** in 92% yield (962 mg, 2.1 mmol) as a white solid.

R_f = 0.80 (Hexanes:EtOAc = 4:1), UV & PMA stain.

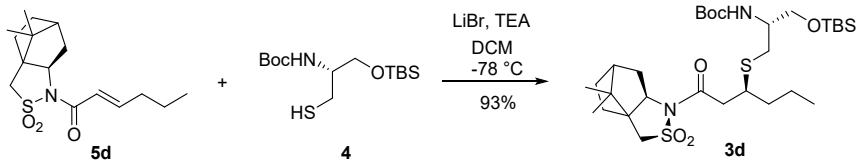
$[\alpha]_D^{28}$ = -25.9 (*c* 5.0, CH_3OH);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (dt, *J* = 15.1, 6.9 Hz, 1H), 6.50 (dt, *J* = 15.0, 1.6 Hz, 1H), 3.87 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.44 (q, *J* = 13.8 Hz, 2H), 2.37 – 2.22 (m, 2H), 2.11 – 1.98 (m, 2H), 1.91 – 1.75 (m, 3H), 1.61 – 1.45 (m, 2H), 1.43 – 1.25 (m, 2H), 1.16 (s, 6H), 1.12 (s, 3H), 0.92 (s, 3H), 0.80 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1, 151.4, 120.6, 73.0, 65.1, 53.2, 48.5, 47.8, 44.8, 43.0, 38.6, 32.9, 29.9, 29.8, 27.7, 26.6, 25.9, 21.0, 20.0, 2.16, -2.0.

HRMS (ESI, *m/z*) for $C_{24}H_{43}NO_4SSiNa^+$ $[M+Na]^+$: Calcd. 492.2574; Found 492.2578.

***tert*-butyl ((2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-(((3*S*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-1-oxohexan-3-yl)thio)propan-2-yl)carbamate**



An oven-dried round-bottom flask was charged with **5d** (50 mg, 0.16 mmol, 1.0 equiv.) and LiBr (14 mg, 0.16 mmol, 1.0 equiv.), and dissolved in degassed anhydrous DCM (1.6 mL, 0.10 M) under argon atmosphere. The solution was stirred for 0.5 h at -78 °C before it was treated sequentially with TEA (22 μL, 0.16 mmol, 1.0 equiv.) and **4** (77 mg, 0.24 mmol, 1.5 equiv.). After being stirred at -78 °C for an additional 9 h, the reaction was carefully quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **3d** in 93% yield (94 mg, 0.14 mmol) as a colorless oil.

R_f = 0.50 (Hexanes:EtOAc = 4:1), UV & PMA stain.

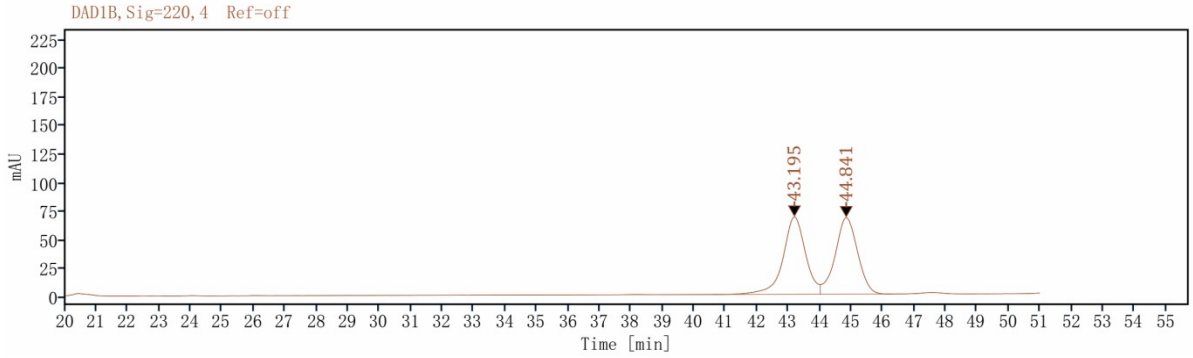
$[\alpha]_D^{26}$ = -90.8 (c 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 – 4.78 (m, 1H), 3.88 (dd, J = 7.6, 4.9 Hz, 1H), 3.76 (t, J = 9.4 Hz, 2H), 3.60 (dd, J = 9.9, 4.5 Hz, 1H), 3.55 – 3.36 (m, 2H), 3.29 – 3.15 (m, 1H), 3.05 (dd, J = 16.1, 8.5 Hz, 1H), 2.82 (dd, J = 16.1, 5.9 Hz, 1H), 2.69 (t, J = 8.1 Hz, 2H), 2.22 – 2.03 (m, 2H), 1.99 – 1.83 (m, 3H), 1.64 – 1.56 (m, 2H), 1.53 – 1.33 (m, 12H), 1.18 (s, 3H), 0.97 (s, 3H), 0.91 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 155.3, 79.2, 65.2, 63.0, 53.1, 51.3, 48.4, 47.8, 44.7, 41.9, 41.5, 38.5, 37.5, 32.9, 31.8, 28.4, 26.5, 25.9, 20.9, 20.0, 19.9, 18.3, 13.9, -5.3, -5.4.

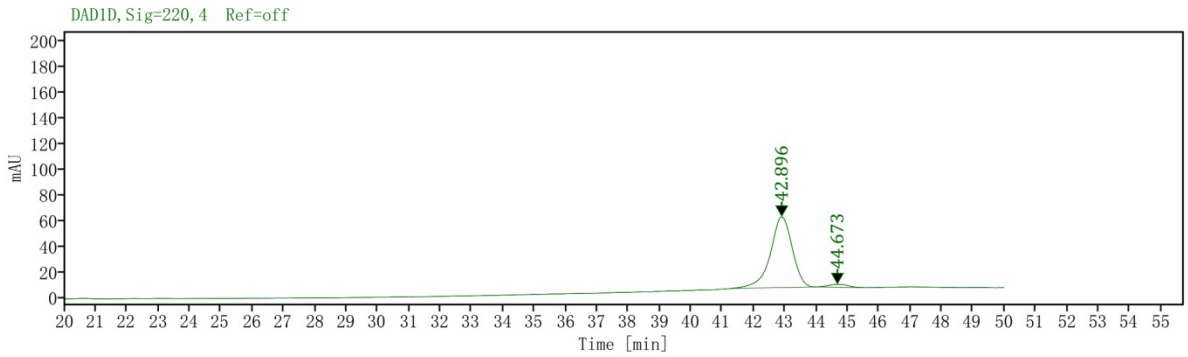
HRMS (ESI, *m/z*) for $C_{30}H_{56}N_2O_6S_2SiNa^+$ $[M+Na]^+$: Calcd. 655.3241; Found 655.3242.

HPLC (100-5-C18 columns, MeCN:H_2O = 92:8, 2.0 mL/min, 220 nm), d.r. = 97:3 .



Signal: DAD1B, Sig=220, 4 Ref=off

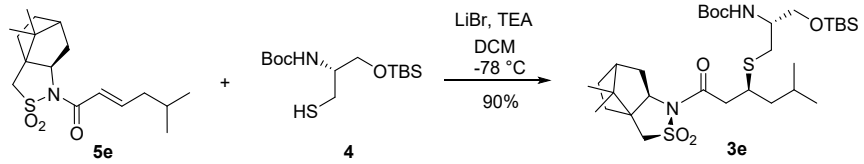
RetTime [min]	Width [min]	Area	Height	Area%
43.195	3.43	3350.87	67.44	50.41
44.841	2.26	3296.07	66.77	49.59
	Totals	6646.94		



Signal: DAD1D, Sig=220, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
42.896	0.73	2666.16	55.10	96.51
44.673	0.55	96.36	2.22	3.49
	Totals	2762.52		

***tert*-butyl ((2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-(((3*S*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-5-methyl-1-oxohexan-3-yl)thio)propan-2-yl)carbamate**



An oven-dried round-bottom flask was charged with **5e** (33 mg, 0.10 mmol, 1.0 equiv.) and LiBr (9.0 mg, 0.10 mmol, 1.0 equiv.), and dissolved in degassed anhydrous DCM (1.0 mL, 0.10 M) under argon atmosphere. The solution was stirred for 0.5 h at -78 °C before it was treated sequentially with TEA (13 μL, 0.10 mmol, 1.0 equiv.) and **4** (48 mg, 0.15 mmol, 1.5 equiv.). After being stirred at -78 °C for an additional 9 h, the reaction was carefully quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **3e** in 90% yield (58 mg, 0.090 mmol) as a colorless oil.

R_f = 0.50 (Hexanes:EtOAc = 6:1), UV & PMA stain.

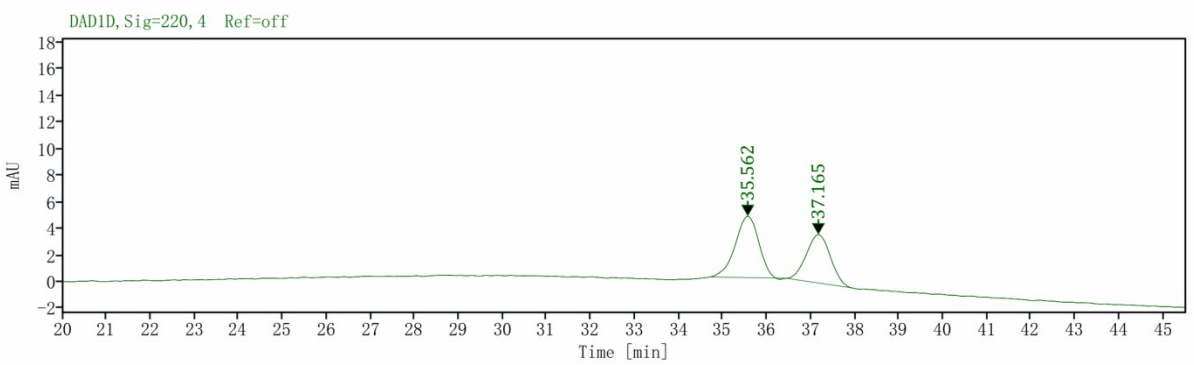
$[\alpha]_D^{26}$ = -60.0 (*c* 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.84 (s, 1H), 3.89 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.75 (d, *J* = 8.9 Hz, 2H), 3.65 – 3.58 (m, 1H), 3.53 – 3.40 (m, 2H), 3.25 (t, *J* = 7.6 Hz, 1H), 3.08 (dd, *J* = 15.9, 8.1 Hz, 1H), 2.80 (dd, *J* = 16.0, 5.9 Hz, 1H), 2.70 (d, *J* = 6.4 Hz, 2H), 2.19 – 2.01 (m, 2H), 1.97 – 1.78 (m, 4H), 1.56 – 1.33 (m, 13H), 1.25 (s, 2H), 1.19 (s, 3H), 0.97 (s, 3H), 0.93 – 0.86 (m, 12H), 0.05 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 155.2, 79.2, 65.3, 63.1, 53.1, 51.4, 48.4, 47.8, 44.8, 42.0, 40.3, 38.5, 32.9, 31.5, 29.7, 28.4, 26.5, 25.9, 25.5, 22.8, 22.1, 20.9, 19.9, 18.3, -5.3, -5.4.

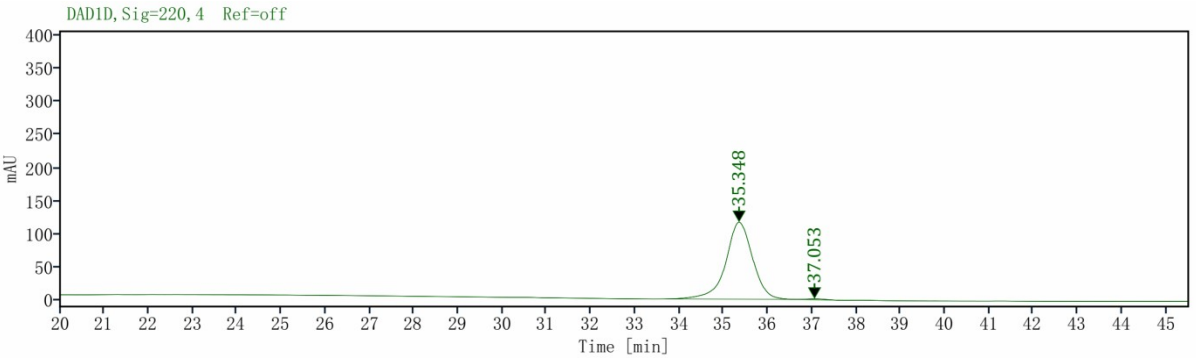
HRMS (ESI, *m/z*) for $C_{31}H_{58}N_2O_6S_2SiNa^+$ $[M+Na]^+$: Calcd. 669.3398; Found 669.3399.

HPLC (100-5-C18 columns, MeCN:H_2O = 95:5, 2.0 mL/min, 220 nm), d.r. = 99:1.



Signal: DAD1D, Sig=220, 4 Ref=off

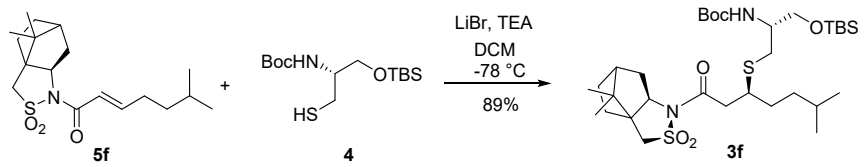
RetTime [min]	Width [min]	Area	Height	Area%
35.562	0.57	170.90	4.61	55.20
37.165	0.56	138.72	3.64	44.80
	Totals	309.62		



Signal: DAD1D, Sig=220, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
35.348	0.63	4916.86	116.37	99.17
37.053	0.45	40.92	1.34	0.83
	Totals	4957.78		

***tert*-butyl ((2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-(((3*S*)-1-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-6-methyl-1-oxoheptan-3-yl)thio)propan-2-yl)carbamate**



An oven-dried round-bottom flask was charged with **5f** (46 mg, 0.14 mmol, 1.0 equiv.) and LiBr (12 mg, 0.14 mmol, 1.0 equiv.), and dissolved in degassed anhydrous DCM (1.0 mL, 0.14 M) under argon atmosphere. The solution was stirred for 0.5 h at -78 °C before it was treated sequentially with of TEA (19 μL, 0.14 mmol, 1.0 equiv.) and **4** (64 mg, 0.21 mmol, 1.5 equiv.). After being stirred at -78 °C for an additional 9 h, the reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **3f** in 90% yield (82 mg, 0.12 mmol) as a colorless oil.

R_f = 0.60 (Hexanes:EtOAc = 6:1), UV & PMA stain.

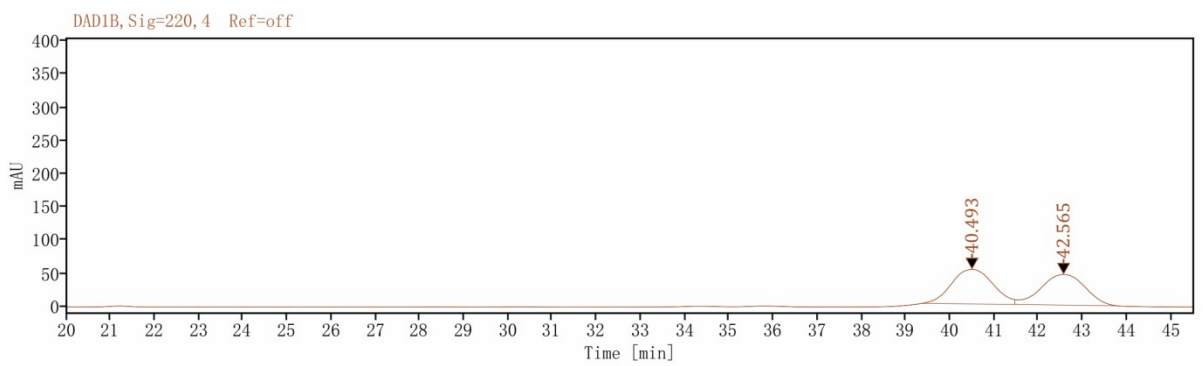
$[\alpha]_D^{26}$ = -46.0 (*c* 1.0, CH_3OH);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (d, *J* = 8.6 Hz, 1H), 3.90 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.84 – 3.73 (m, 2H), 3.66 – 3.56 (m, 1H), 3.55 – 3.40 (m, 2H), 3.29 – 3.15 (m, 1H), 3.07 (dd, *J* = 16.0, 8.4 Hz, 1H), 2.84 (dd, *J* = 16.0, 5.7 Hz, 1H), 2.76 – 2.64 (m, 2H), 2.20 – 2.05 (m, 2H), 1.98 – 1.82 (m, 3H), 1.57 – 1.51 (m, 1H), 1.46 (s, 9H), 1.40 – 1.25 (m, 4H), 1.21 (s, 3H), 0.99 (s, 4H), 0.92 – 0.87 (m, 15H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 155.4, 65.3, 63.1, 53.2, 51.4, 48.6, 47.9, 44.8, 42.6, 41.6, 38.6, 35.9, 33.3, 33.0, 32.0, 29.8, 28.6, 28.1, 26.6, 26.0, 22.8, 22.7, 21.0, 20.0, 18.4. -5.2, -5.3.

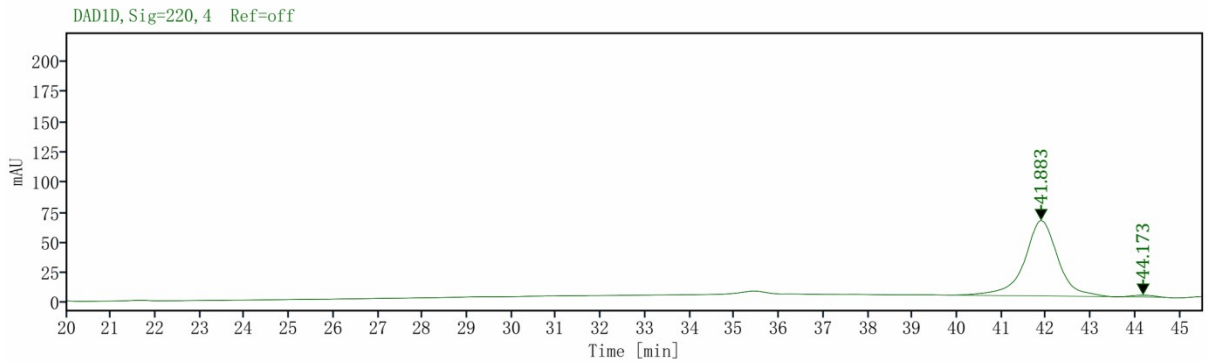
HRMS (ESI, *m/z*) for $C_{32}H_{60}N_2O_6S_2SiNa^+$ $[M+Na]^+$: Calcd. 683.3553; Found 683.3554.

HPLC (100-5-C18 columns, MeCN:H_2O = 95:5, 2.0 mL/min, 220 nm), d.r. = 98:2.



Signal: DAD1B, Sig=220, 4 Ref=off

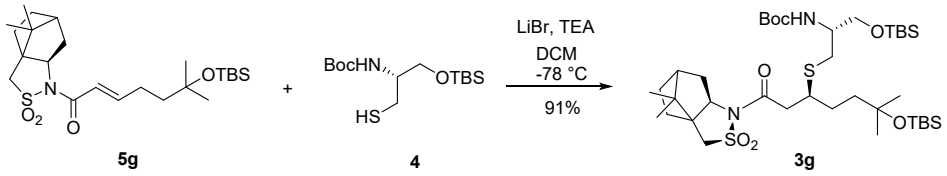
RetTime [min]	Width [min]	Area	Height	Area%
40.493	1.03	3394.20	52.10	51.47
42.565	1.10	3200.17	46.10	48.53
	Totals	6594.37		



Signal: DAD1D, Sig=220, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
41.883	0.78	3255.30	62.41	98.47
44.173	0.46	50.47	1.50	1.53
	Totals	3305.77		

***tert*-butyl ((6*R*,9*S*)-9-(2-((7*aR*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-oxoethyl)-2,2,3,3,12,12,14,14,15,15-decamethyl-4,13-dioxa-8-thia-3,14-disilahexadecan-6-yl)carbamate**



5g 4 3g

An oven-dried round-bottom flask was charged with **5g** (50 mg, 0.11 mmol, 1.0 equiv.) and LiBr (10 mg, 0.11 mmol, 1.0 equiv.), and dissolved in degassed anhydrous DCM (1.0 mL, 0.11 M) under argon atmosphere. The solution was stirred for 0.5 h at -78 °C before it was treated sequentially with TEA (16 μL, 0.11 mmol, 1.0 equiv.) and **4** (52 mg, 0.16 mmol, 1.5 equiv.). The reaction mixture was further stirred at -78 °C for 9 h, then quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/9) to furnish **3g** in 91% yield (79 mg, 0.10 mmol) as a colorless oil.

R_f = 0.60 (Hexanes:EtOAc = 6:1), UV & PMA stain.

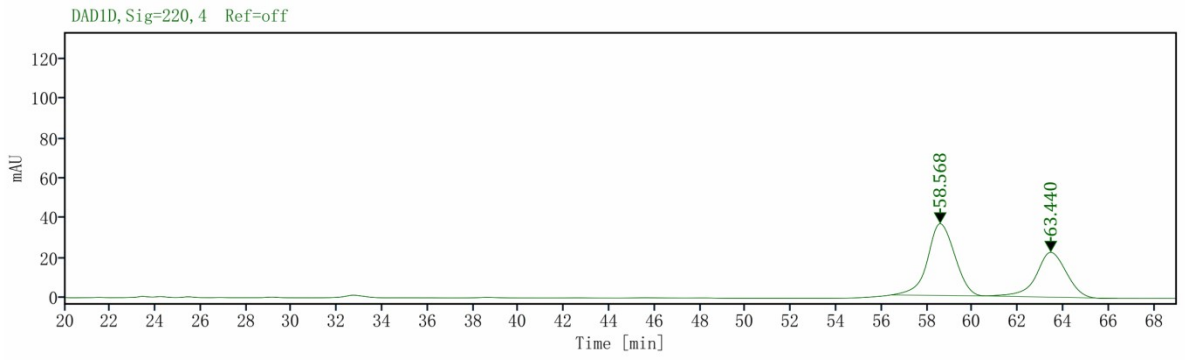
$[\alpha]_D^{26}$ = -24.1 (*c* 1.0, CH_3OH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (s, 1H), 3.88 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.77 (s, 2H), 3.61 (s, 1H), 3.54 – 3.39 (m, 2H), 3.28 – 3.15 (m, 1H), 3.05 (dd, *J* = 16.0, 8.6 Hz, 1H), 2.80 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.75 – 2.60 (m, 2H), 2.20 – 2.03 (m, 2H), 1.89 (dd, *J* = 20.5, 9.9 Hz, 3H), 1.78 – 1.67 (m, 3H), 1.53 – 1.34 (m, 13H), 1.20 (s, 9H), 0.97 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.06 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 155.2, 79.2, 73.2, 65.2, 63.0, 53.1, 51.3, 48.4, 47.8, 44.8, 42.7, 41.8, 41.5, 38.5, 32.9, 31.9, 30.0, 29.7, 28.5, 26.5, 25.9, 22.7, 20.9, 19.9, 18.3, 18.1, 14.1, -2.0, -5.3, -5.4.

HRMS (ESI, *m/z*) for $C_{38}H_{74}N_2O_7S_2Si_2Na^+$ $[M+Na]^+$: Calcd. 813.4368; Found 813.4367.

HPLC (100-5-C18 columns, MeCN:H_2O = 100:0, 2.0 mL/min, 220 nm), d.r. = 96:4.



Signal: DAD1D, Sig=220, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
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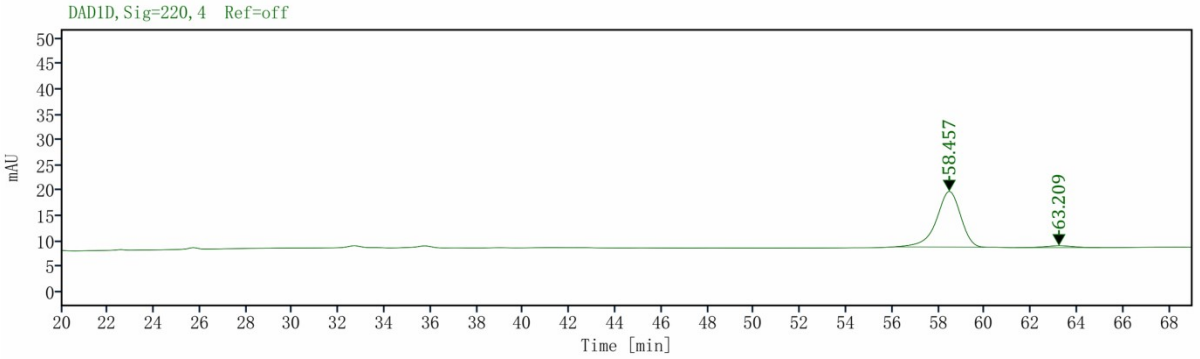
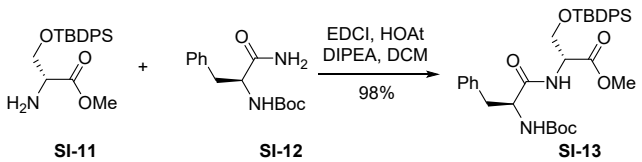
63.440	1.36	2094.14	22.59	42.93
	Totals	4878.53		



Signal: DAD1D, Sig=220, 4 Ref=off

RetTime [min]	Width [min]	Area	Height	Area%
58.457	1.05	803.91	11.01	96.49
63.209	0.96	29.23	0.36	3.51
	Totals	833.14		

Methyl *N*-((*tert*-butoxycarbonyl)-*L*-phenylalanyl)-*O*-(*tert*-butyldiphenylsilyl)-*D*-serinate



To a solution of **SI-11** (100 mg, 0.28 mmol, 1.0 equiv.) in DCM (5.0 mL, 0.060 M) at 0 °C was added **SI-12** (148 mg, 0.56 mmol, 2.0 equiv.) followed by addition of DIPEA (0.25 mL, 1.4 mmol, 5.0 equiv.), EDCI (134 mg, 0.70 mmol, 2.5 equiv.) and HOAt (38 mg, 0.28 mmol, 1.0 equiv.). The reaction mixture was stirred for 9 h at room temperature, then quenched with saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) to furnish **SI-13** in 98% yield (165 mg, 0.27 mmol) as a yellow solid.

R_f = 0.40 (Hexanes:EtOAc = 4:1), UV & PMA stain.

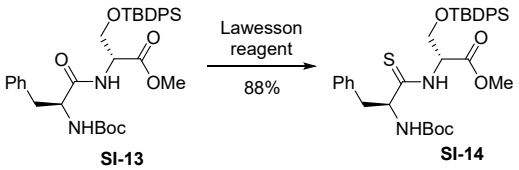
$[\alpha]_D^{25}$ = -5.7 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (dt, *J* = 8.1, 1.8 Hz, 4H), 7.51 – 7.36 (m, 6H), 7.31 – 7.14 (m, 4H), 6.99 (d, *J* = 9.4 Hz, 1H), 5.07 (d, *J* = 8.4 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.07 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.76 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.71 (s, 3H), 3.19 (dd, *J* = 14.0, 6.2 Hz, 1H), 3.03 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.38 (s, 9H), 1.04 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 170.6, 155.5, 136.7, 135.5, 135.5, 132.7, 132.6, 130.0, 129.3, 128.6, 127.9, 127.8, 126.8, 80.1, 64.1, 55.6, 54.0, 52.3, 38.3, 28.2, 26.7, 19.2.

HRMS (ESI, *m/z*) for $C_{34}H_{44}N_2O_6SiNa^+$ $[M + Na]^+$: Calcd. 627.2861; Found 627.2866.

Methyl *N*-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanethioyl)-*O*-(*tert*-butyldiphenylsilyl)-*D*-serinate



To a solution of **SI-13** (2.7 g, 4.4 mmol, 1.0 equiv.) in PhMe (15 mL, 0.30 M) at 0 °C was added the Lawesson reagent (1.0 g, 2.4 mmol, 0.55 equiv.). The reaction mixture was heated to 70 °C and stirred for 9 h before beingcooled to room temperature, and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) to furnish **SI-14** in 88% yield (2.4 g, 3.9 mmol) as a yellow solid.

R_f = 0.60 (Hexanes:EtOAc = 4:1), UV & PMA stain.

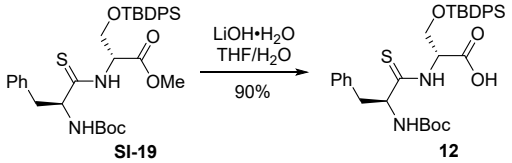
$[\alpha]_D^{27}$ = -4.6 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.61 – 7.53 (m, 4H), 7.49 – 7.43 (m, 2H), 7.40 (td, *J* = 7.0, 3.8 Hz, 4H), 7.26 – 7.20 (m, 4H), 7.16 (dt, *J* = 6.2, 3.0 Hz, 1H), 5.24 (s, 1H), 5.13 (dt, *J* = 7.2, 3.2 Hz, 1H), 4.72 (s, 1H), 4.05 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.76 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.72 (s, 3H), 3.29 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.13 (t, *J* = 10.1 Hz, 1H), 1.37 (s, 9H), 1.03 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.0, 169.7, 155.4, 137.0, 135.6, 135.6, 132.6, 132.5, 130.2, 129.4, 128.6, 128.0, 128.0, 126.9, 80.1, 63.0, 62.3, 59.4, 52.5, 42.1, 28.4, 26.9, 19.3.

HRMS (ESI, *m/z*) for $C_{34}H_{44}N_2O_5SSiNa^+$ $[M + Na]^+$: Calcd. 643.2638; Found 643.2637.

***N*-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanethioyl)-*O*-(*tert*-butyldiphenylsilyl)-*D*-serine**



To a solution of **SI-14** (458 mg, 0.74 mmol, 1.0 equiv.) in 10 mL (0.070 M) of a 1:1 mixture of THF:H_2O at 0 °C, LiOH·H_2O (155 mg, 3.7 mmol, 5.0 equiv.) was added. After being stirred for 9 h at room temperature, the solvents were removed in vacuo, and the residue was diluted with water (5 mL),acidified to pH=2 with HCl (1.0 M in water) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired acid **12** in 90% yield (403 mg, 0.67 mmol) as a yellow solid.

R_f = 0.30 (Hexanes:EtOAc = 4:1), UV & PMA stain.

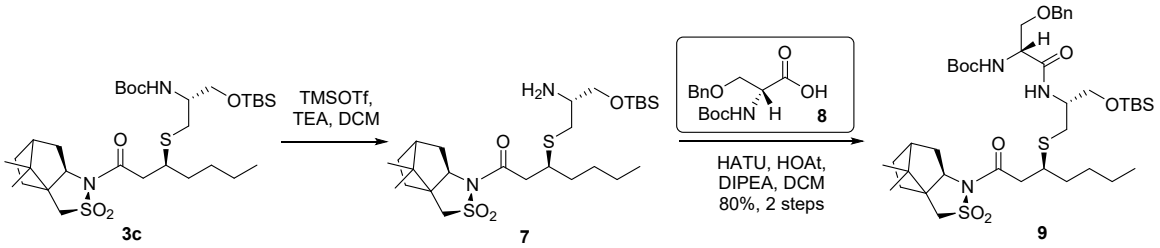
$[\alpha]_D^{25}$ = -7.3 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (d, *J* = 6.3 Hz, 1H), 7.90 – 7.72 (m, 4H), 7.64 – 7.40 (m, 6H), 7.31 – 7.25 (m, 2H), 7.21 – 7.16 (m, 3H), 5.95 (d, *J* = 9.8 Hz, 1H), 5.69 (td, *J* = 9.4, 5.5 Hz, 1H), 5.32 – 5.17 (m, 1H), 4.26 (dd, *J* = 10.4, 4.2 Hz, 1H), 4.14 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.18 – 2.97 (m, 2H), 1.42 (s, 9H), 1.24 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9, 172.7, 156.0, 136.8, 135.9, 135.8, 133.1, 133.0, 130.1, 129.7, 128.6, 128.1, 126.9, 81.2, 61.9, 60.5, 59.6, 44.5, 28.5, 27.0, 19.6.

HRMS (ESI, *m/z*) for $C_{33}H_{42}N_2O_5SSiNa^+$ $[M + Na]^+$: Calcd. 629.2476; Found 629.2477.

***tert*-butyl ((4*R*,7*R*)-7-((((2*S*)-1-((7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[c]isothiazol-1(4*H*)-yl)-1-oxoheptan-2-yl)thio)methyl)-10,10,11,11-tetramethyl-5-oxo-1-phenyl-2,9-dioxa-6-aza-10-siladodecan-4-yl)carbamate**



To a solution of **3c** (500 mg, 0.77 mmol, 1.0 equiv.) in DCM (20 mL, 0.039 M) at 0 °C, TEA (0.86 mL, 6.2 mmol, 8.0 equiv.) was added, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.70 mL, 3.9 mmol, 5.0 equiv.). After being stirred for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to afford the crude material **7**, which was used directly in the next step without further purification. To a solution of above **7** (0.77 mmol 1.0 equiv.) in DCM (20 mL 0.039 M) at 0 °C was added acid **8** (343 mg, 1.16 mmol, 1.5 equiv.) followed by addition of DIPEA (0.70 mL, 3.9 mmol, 5.0 equiv.), HATU (600 mg, 1.6 mmol, 2.0 equiv.) and HOAt (106 mg, 0.77 mmol, 1.0 equiv.). The reaction mixture was stirred for 9 h at room temperature, before being quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) providing 510 mg (0.62 mmol) of amide **9** (80% yield for 2 steps) as a colorless oil.

R_f = 0.30 (Hexanes:EtOAc = 4:1), UV & PMA stain.

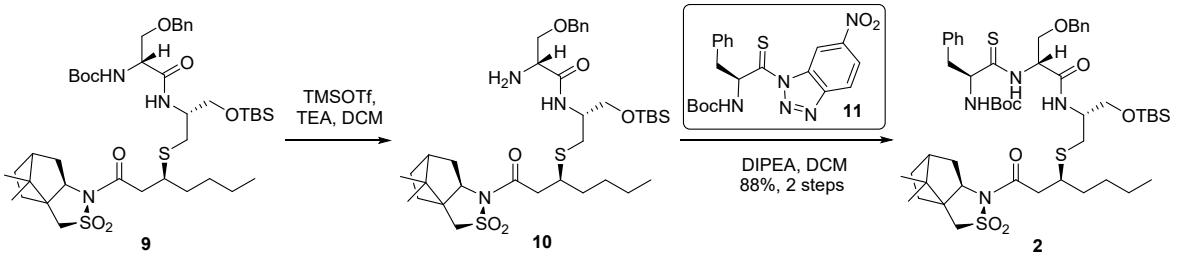
$[\alpha]_D^{27}$ = -12.7 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, CD_3OD): δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 4.61 – 4.50 (m, 2H), 4.30 (s, 1H), 4.08 – 3.98 (m, 1H), 3.90 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.84 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.75 – 3.67 (m, 2H), 3.68 – 3.58 (m, 3H), 3.23 (dt, *J* = 7.8, 6.1 Hz, 1H), 3.05 (dd, *J* = 15.9, 8.2 Hz, 1H), 2.77 (dd, *J* = 15.7, 6.1 Hz, 2H), 2.66 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.04 (dd, *J* = 13.8, 7.9 Hz, 1H), 1.99 – 1.87 (m, 2H), 1.85 – 1.81 (m, 1H), 1.69 – 1.53 (m, 2H), 1.51 – 1.38 (m, 11H), 1.40 – 1.29 (m, 4H), 1.20 (s, 3H), 1.02 (s, 3H), 0.93 (s, 12H), 0.09 (s, 6H).

^{13}C NMR (101 MHz, CD_3OD): δ 171.1, 170.2, 156.3, 138.0, 128.2, 127.6, 127.5, 79.6, 73.0, 70.0, 65.1, 62.8, 54.8, 52.4, 51.1, 51.0, 48.5, 45.0, 41.5, 41.4, 38.4, 34.7, 32.3, 30.8, 28.8, 27.5, 26.1, 25.3, 22.3, 20.5, 19.0, 17.9, 13.2, -6.3, -6.3.

HRMS (ESI, *m/z*) for $C_{41}H_{69}N_3O_8S_2SiNa^+$ $[M + Na]^+$: Calcd. 846.4188; Found 846.4189.

***tert*-butyl ((6*R*,9*R*,12*S*)-9-((benzyloxy)methyl)-6-((((3*S*)-1-((7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[c]isothiazol-1(4*H*)-yl)-1-oxoheptan-3-yl)thio)methyl)-2,2,3,3-tetramethyl-8-oxo-13-phenyl-11-thioxo-4-oxa-7,10-diaza-3-silatridecan-12-yl)carbamate**



To a solution of **9** (67 mg, 0.081 mmol, 1.0 equiv.) in DCM (3.0 mL, 0.027 M) at 0 °C, TEA (0.30 mL, 2.0 mmol, 25 equiv.) was added, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.15 mL, 0.81 mmol 10 equiv.). The reaction mixture was stirred for 1 h at room temperature, then quenched with saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to afford the crude product **10**, which was used directly in the next step without further purification.

To a solution of above **10** (58 mg, 0.081 mmol 1.0 equiv.) in DCM (3 mL 0.027 M) at 0 °C was added **11** (104 mg, 0.24 mmol, 3.0 equiv.) followed by addition of DIPEA (0.10 mL, 0.41 mmol, 5.0 equiv.). After being stirred for 9 h at room temperature, the reaction mixture was quenched with saturated

aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/4) to furnish thioamide **2** in 88% yield for 2 steps (70 mg, 0.070 mmol) as a colorless oil.

R_f = 0.30 (Hexanes:EtOAc = 4:1), UV & PMA stain.

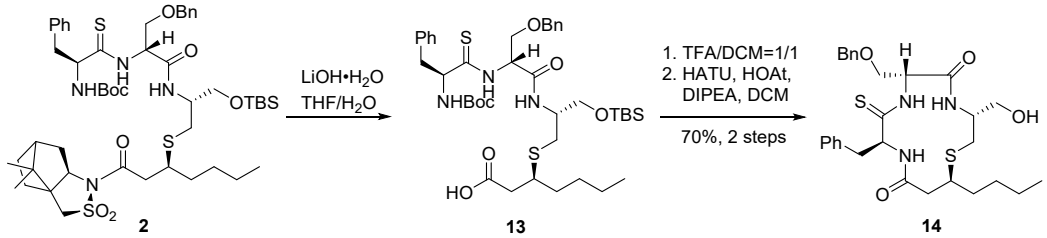
$[\alpha]_D^{28}$ = -8.8 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.1 Hz, 1H), 7.44 – 7.25 (m, 5H), 7.22 – 7.10 (m, 5H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.42 (s, 1H), 4.91 (ddd, *J* = 10.3, 7.2, 3.5 Hz, 1H), 4.55 (s, 1H), 4.50 (s, 2H), 4.03 (dq, *J* = 11.4, 3.5 Hz, 1H), 3.88 (dd, *J* = 7.6, 5.0 Hz, 1H), 3.81 (dd, *J* = 10.1, 2.8 Hz, 1H), 3.71 (dd, *J* = 9.3, 3.6 Hz, 1H), 3.57 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.52 – 3.38 (m, 2H), 3.27 – 3.18 (m, 1H), 3.08 (q, *J* = 6.3, 4.5 Hz, 2H), 3.01 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.81 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.63 (d, *J* = 6.9 Hz, 2H), 2.16 – 2.04 (m, 2H), 1.95 – 1.78 (m, 4H), 1.61 (q, *J* = 7.3 Hz, 2H), 1.44 – 1.37 (m, 11H), 1.38 – 1.24 (m, 5H), 1.18 (s, 3H), 0.97 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.02 (d, *J* = 2.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.2, 169.9, 168.1, 154.8, 137.3, 136.5, 129.2, 128.7, 128.5, 128.0, 127.9, 127.0, 80.2, 73.3, 67.3, 65.2, 63.0, 62.5, 56.9, 53.1, 50.8, 48.5, 47.8, 44.8, 42.5, 41.9, 41.3, 38.5, 35.0, 32.9, 31.1, 28.9, 28.3, 26.5, 25.9, 22.5, 20.9, 19.9, 18.3, 14.1, -5.3, -5.4.

HRMS (ESI, *m/z*) for $C_{50}H_{78}N_4O_8S_3SiNa^+$ $[M + Na]^+$: Calcd. 1009.4643; Found 1009.4648.

(3*R*,6*R*,9*S*,13*S*)-9-benzyl-6-((benzyloxy)methyl)-13-butyl-3-(hydroxymethyl)-8-thioxo-1-thia-4,7,10-triazacyclotridecane-5,11-dione



To a solution of **2** (265 mg, 0.27 mmol, 1.0 equiv.) in 10 mL (0.30 M) of a 1:1mixture of THF:H_2O, LiOH·H_2O (113 mg, 2.7 mmol, 10 equiv.) was added at 0 °C. After being stirred for 9 h at room temperature, the reaction mixture was diluted with water (5 mL), buffered to pH=11 with NaOH (1.0 M in water), evaporation of THF, and extracted with DCM (10 mL) to remove the Oppolzer's sultam. The

aqueous layer was acidified to pH=2 with HCl (1.0 M in water), and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired acid **13** as a colorless oil, which was used directly in the next step without further purification.

To a solution of **13** (0.27 mmol, 1.0 equiv.) in DCM (3 mL 0.090 M) at 0 °C was added TFA (3.0 mL), stirred for 1 h at room temperature, and then the concentrated in *vacuo* to afford the crude amino acid, which was used directly in the next step without further purification.

To a solution of above crude product in DCM (270 mL 0.0010 M) at 0 °C was added sequentially DIPEA (0.48 mL, 2.7 mmol, 10 equiv.), HATU (522 mg, 1.4 mmol, 5.0 equiv.) and HOAt (73 mg, 0.54 mmol, 2.0 equiv.). After being stirred for 72 h at room temperature, the reaction mixture was quenched by the addition of an aqueous solution of citric acid (4%wt, 10 mL) and then concentrated in *vacuo*. The residue was dissolved in EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/1) providing the cyclized product **14** in 70% yield for 2 steps (105 mg, 0.19 mmol) as a white solid.

R_f = 0.60 (Hexanes:EtOAc = 1:1), UV & PMA stain.

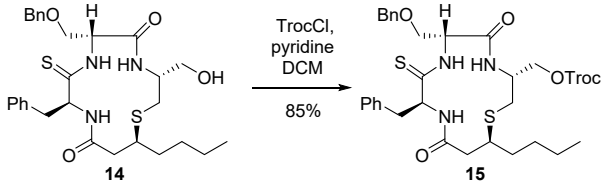
$[\alpha]_D^{25}$ = -14.2 (*c* 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, *J* = 8.2 Hz, 1H), 7.65 – 6.96 (m, 10H), 6.81 (d, *J* = 4.3 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H), 5.04 (dt, *J* = 8.3, 3.1 Hz, 1H), 4.81 (q, *J* = 7.9 Hz, 1H), 4.53 (q, *J* = 12.1 Hz, 2H), 4.07 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.79 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.65 (dt, *J* = 12.4, 4.0 Hz, 1H), 3.58 – 3.45 (m, 2H), 3.36 – 3.26 (m, 2H), 3.16 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.96 – 2.87 (m, 1H), 2.60 (dd, *J* = 15.2, 3.7 Hz, 1H), 2.51 (t, *J* = 12.4 Hz, 1H), 2.13 (dd, *J* = 15.4, 12.6 Hz, 1H), 1.63 – 1.45 (m, 3H), 1.37 – 1.28 (m, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.5, 173.7, 169.7, 137.1, 136.2, 129.2, 128.7, 128.7, 128.2, 127.9, 127.1, 73.5, 68.7, 65.8, 60.7, 59.5, 53.4, 49.5, 43.7, 39.0, 38.0, 37.6, 29.5, 22.4, 14.0.

HRMS (ESI, *m/z*) for $C_{29}H_{39}N_3O_4S_2Na^+$ $[M + Na]^+$: Calcd. 580.2274; Found 580.2277.

((3*R*,6*R*,9*S*,13*S*)-9-benzyl-6-((benzyloxy)methyl)-13-butyl-5,11-dioxo-8-thioxo-1-thia-4,7,10-triazacyclotridecan-3-yl)methyl (2,2,2-trichloroethyl) carbonate



To a solution **14** (18 mg, 0.032 mmol, 1.0 equiv.) in DCM (5.0 mL, 0.0060 M) at 0 °C were added sequentially TrocCl (19 µL, 0.13mmol, 4.0 equiv.), pyridine (27 µL, 0.33 mmol, 10 equiv.) After being stirred for 1 h, the reaction was quenched by addition of water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/3) to afford**15** in 85% yield (17 mg, 0.027 mmol) as a white solid.

R_f = 0.50 (Hexanes:EtOAc = 3:1), UV & PMA stain.

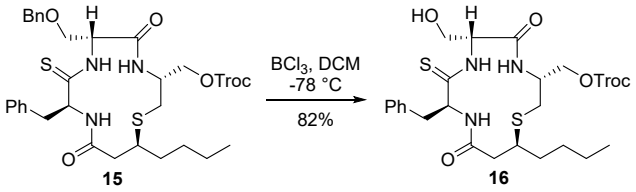
$[\alpha]_D^{26}$ = -11.8 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.20 (m, 10H), 6.76 (d, *J* = 5.0 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.04 (dt, *J* = 8.1, 3.4 Hz, 1H), 4.82 (q, *J* = 7.9 Hz, 1H), 4.78 – 4.64 (m, 2H), 4.51 (q, *J* = 12.2 Hz, 2H), 4.41 – 4.34 (m, 2H), 4.00 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.54 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.40 (dd, *J* = 12.7, 3.2 Hz, 1H), 3.33 (dd, *J* = 13.8, 7.9 Hz, 1H), 3.17 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.93 (ddt, *J* = 12.7, 9.0, 4.7 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.18 (dd, *J* = 15.5, 12.6 Hz, 1H), 1.70 – 1.47 (m, 3H), 1.42 – 1.30 (m, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.9, 174.0, 169.0, 153.9, 137.4, 136.2, 129.3, 128.8, 128.8, 128.2, 127.8, 127.2, 94.5, 77.4, 77.0, 73.4, 69.0, 68.5, 61.2, 59.8, 49.3, 49.2, 43.8, 39.2, 37.5, 29.6, 22.6, 14.2.

HRMS (ESI, *m/z*) for $C_{32}H_{40}Cl_3N_3O_6S_2Na^+$ $[M + Na]^+$: Calcd. 754.1316; Found 754.1323.

((3*R*,6*R*,9*S*,13*S*)-9-benzyl-13-butyl-6-(hydroxymethyl)-5,11-dioxo-8-thioxo-1-thia-4,7,10-triazacyclotridecan-3-yl)methyl (2,2,2-trichloroethyl) carbonate



To a solution of **15** (20 mg, 0.028 mmol, 1.0 equiv.) in anhydrous DCM (3 mL, 0.010 M) was added BCl_3 (0.30 mL, 0.28 mmol, 10 equiv.,1 M in DCM) at -78 °C under argon atmosphere. After being stirred at -78 °C for 3 h, then recooled –90 °C, the reaction mixture was quenched by slow addition of MeOH (0.5 mL) via syringe while maintaining the internal temperature below-78 °C. The mixture was allowed to room temperature, and then concentrated in *vacuo* to afford a solid residue, which was redissolved in DCM (3 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/2) to **16** in 82% yield (15 mg, 0.023 mmol) as a white solid.

R_f = 0.30 (Hexanes:EtOAc = 2:1), UV & PMA stain.

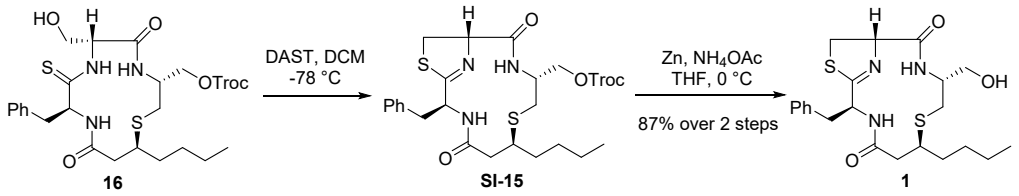
$[\alpha]_D^{24}$ = +9.4 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 8.1 Hz, 1H), 7.35 – 7.22 (m, 5H), 6.93 (d, *J* = 4.6 Hz, 1H), 6.33 (d, *J* = 8.4 Hz, 1H), 5.00 – 4.88 (m, 2H), 4.84 (q, *J* = 7.9 Hz, 1H), 4.78 (s, 2H), 4.28 (dd, *J* = 11.9, 2.0 Hz, 1H), 4.11 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.81 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.67 – 3.55 (m, 1H), 3.41 – 3.28 (m, 2H), 3.17 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.92 (ddt, *J* = 12.8, 8.9, 4.6 Hz, 2H), 2.76 – 2.56 (m, 2H), 2.23 – 2.10 (m, 1H), 1.55 (tt, *J* = 11.2, 5.1 Hz, 3H), 1.34 (t, *J* = 6.4 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.8, 174.0, 169.9, 154.9, 136.2, 129.3, 128.8, 127.3, 94.3, 69.2, 62.2, 61.4, 61.3, 50.0, 49.6, 43.7, 39.1, 37.6, 37.1, 29.8, 29.6, 22.6, 14.2.

HRMS (ESI, *m/z*) for $C_{25}H_{34}Cl_3N_3O_6S_2Na^+$ $[M+Na]^+$: Calcd. 664.0847; Found 664.0852.

(1*S*,4*R*,7*S*,11*S*,*Z*)-11-benzyl-7-butyl-4-(hydroxymethyl)-6,13-dithia-3,10,15-triazabicyclo[10.2.1]pentadec-12(15)-ene-2,9-dione



To a solution of **16** (15 mg, 0.023 mmol, 1.0 equiv.) in DCM (5 mL, 0.0040 M), DAST (18 μL, 0.14 mmol, 6.0 equiv.) was dropwise added at -78 °C. The reaction mixture was slowly warmed to -50 °C then poured to ice-water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to afford thiazoline **SI-15**.

To a solution of above **SI-15** (0.023 mmol, 1.0 equiv.) in THF (3.5 mL), activated Zn powder (200 mg) was added at 0 °C under an argon atmosphere, followed by dropwise addition of an aqueous solution of NH_4OAc (1.0 M, 1.2 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was filtered through a pad of Celite and eluted with EtOAc (20 mL). The combined organics were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was subjected to flash column chromatography (EtOAc/Hexanes = 1/1) to afford 9 mg of thioamycolamide A (**1**) in 87% yield (for 2 steps) as a white solid.

R_f = 0.20 (Hexanes:EtOAc = 1:1), UV & PMA stain.

$[\alpha]_D^{24}$ = -76.6 (*c* 0.5, CH_3OH);

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.84 (d, *J* = 6.7 Hz, 1H), 7.35 – 7.27 (m, 4H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.77 (d, *J* = 5.7 Hz, 1H), 5.08 (t, *J* = 6.7 Hz, 1H), 4.82 (dd, *J* = 6.4, 5.0 Hz, 1H), 4.54 (ddd, *J* = 9.9, 6.8, 5.1 Hz, 1H), 3.56 (d, *J* = 7.1 Hz, 2H), 3.51 (dt, *J* = 10.7, 4.6 Hz, 1H), 3.39 (tq, *J* = 9.2, 4.4 Hz, 1H), 3.21 (ddd, *J* = 10.6, 8.0, 6.6 Hz, 1H), 3.10 (dd, *J* = 13.0, 4.3 Hz, 1H), 3.03 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.95 (dd, *J* = 13.9, 9.9 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.79 (dd, *J* = 13.1, 8.7 Hz, 1H), 2.39 (d, *J* = 8.8 Hz, 2H), 1.55 (ddt, *J* = 9.1, 6.8, 4.3 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.45 – 1.40 (m, 1H), 1.41 – 1.31 (m, 1H), 1.33 – 1.21 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 177.7, 171.6, 170.3, 137.4, 129.1, 128.3, 126.7, 77.7, 62.0, 54.3, 50.7, 45.8, 42.5, 37.7, 36.9, 36.9, 34.9, 28.8, 21.9, 14.0.

HRMS (ESI, *m/z*) for $C_{22}H_{31}N_3O_3S_2Na^+$ $[M+Na]^+$: Calcd. 472.1699; Found 472.1701.

III. Comparison of ^{1}H NMR and ^{13}C NMR Data of Thioamycolamide A

Table II: Comparison of ^{1}H NMR Data of Thioamycolamide A

(Natural Product and Synthetic Sample)

No.	Thioamycolamide A		
	Natural (δ_1) **δH (mult., *J*, Hz)**	**Synthetic (δ_2)** **δH (mult., *J*, Hz)**	**$\Delta_\delta=\delta_1-\delta_2$** **δH (mult., *J*, Hz)**
1	2.79 (dd, 13.0, 8.8) 3.10 (dd, 13.0, 4.3)	2.79 (dd, 13.1, 8.7) 3.10 (dd, 13.0, 4.3)	0.00 0.00
2	3.39 (m)	3.39 (m)	0.00
3	3.21 (m) 3.51 (m)	3.21 (ddd, 10.6, 8.0, 6.6) 3.51 (dt, 10.7, 4.6)	0.00 0.00
4			
5	5.08 (t, 6.7)	5.08 (t, 6.7)	0.00
6	3.56 (d, 6.7)	3.56 (d, 7.1)	0.00
7			
8	4.54 (m)	4.54 (m)	0.00
9	2.96 (dd, 13.9, 9.9) 3.03 (dd, 13.9, 5.0)	2.95 (dd, 13.9, 9.9) 3.03 (dd, 13.9, 5.2)	0.01 0.00
10			
11/15	7.32 (d, 7.9)	7.31 (m)	0.01
12/14	7.29 (t, 7.6)	7.31 (m)	-0.02
13	7.22 (t, 7.1)	7.22 (t, 7.1)	0.00
16			
17	2.39 (d, 8.3)	2.39 (d, 8.8)	0.00
18	2.90 (m)	2.90 (m)	0.00
19	1.42 (m) 1.54 (m)	1.42 (m) 1.55 (m)	0.00 -0.01
20	1.35 (m) 1.45 (m)	1.36 (m) 1.46 (m)	-0.01 -0.01
21	1.28 (m)	1.27 (m)	0.01
22	0.87 (t, 7.3)	0.87 (t, 7.3)	0.00
2-NH	6.77 (d, 5.7)	6.77 (d, 5.7)	0.00
3-OH	4.82 (s)	4.82 (dd, 6.4, 5.0)	0.00
8-NH	8.85 (d, 6.7)	8.84 (d, 6.7)	0.01

Table III: Comparison of ^{13}C NMR Data of Thioamycolamide A

(Natural Product and Synthetic Sample)

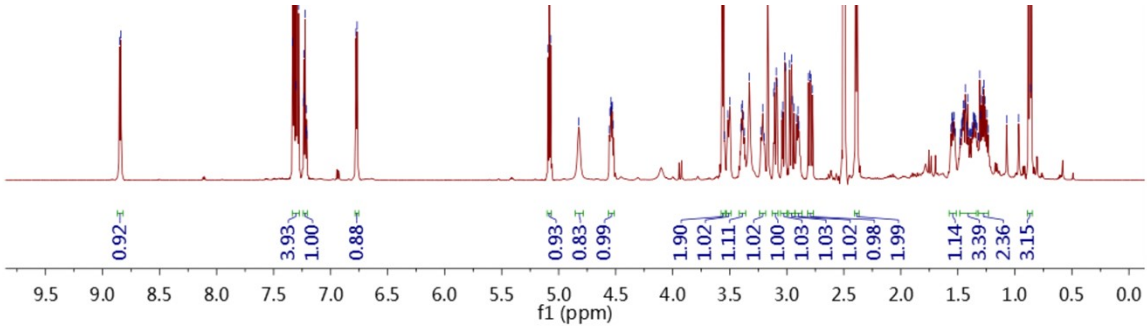
No.	Thioamycolamide A		
	Natural (δ_3)	**Synthetic (δ_4)**	**$\Delta_\delta=\delta_3-\delta_4$**
1	34.9	34.9	0.0

2	50.6	50.7	-0.1
3	61.9	62.0	-0.1
4	170.2	170.3	-0.1
5	77.7	77.7	0.0
6	36.8	36.9	-0.1
7	177.7	177.7	0.0
8	54.3	54.3	0.0
9	37.6	37.7	-0.1
10	137.4	137.4	0.0
11/15	129.1	129.1	0.0
12/14	128.3	128.3	0.0
13	126.6	126.7	-0.1
16	171.6	171.6	0.0
17	42.5	42.5	0.0
18	45.7	45.8	-0.1
19	36.8	36.9	-0.1
20	28.8	28.8	0.0
21	21.8	21.9	-0.1
22	14.0	14.0	0.0
2-NH			
3-OH			
8-NH			

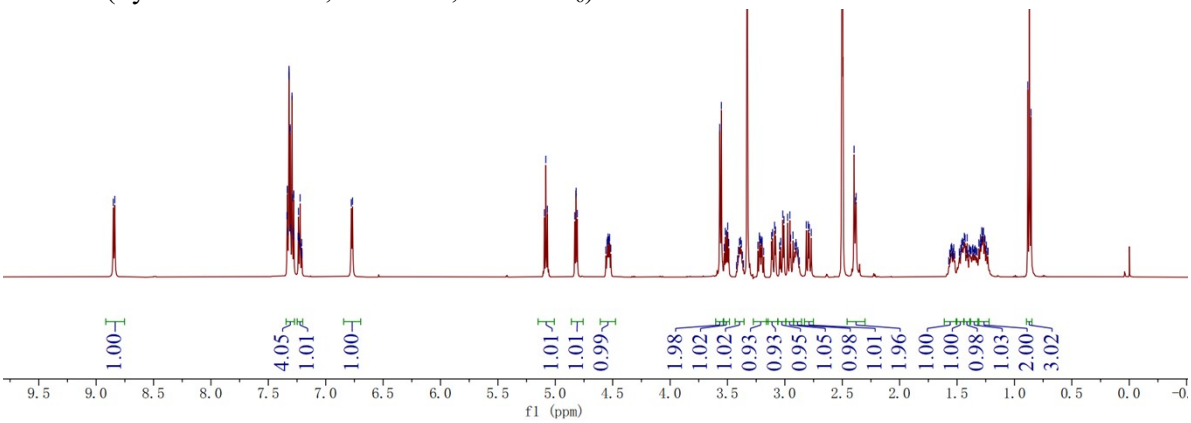
IV. Comparison of NMR Spectra of Natural and Synthetic Thioamycolamide A

Comparison of NMR Spectra of Natural and Synthetic Thioamycolamide A

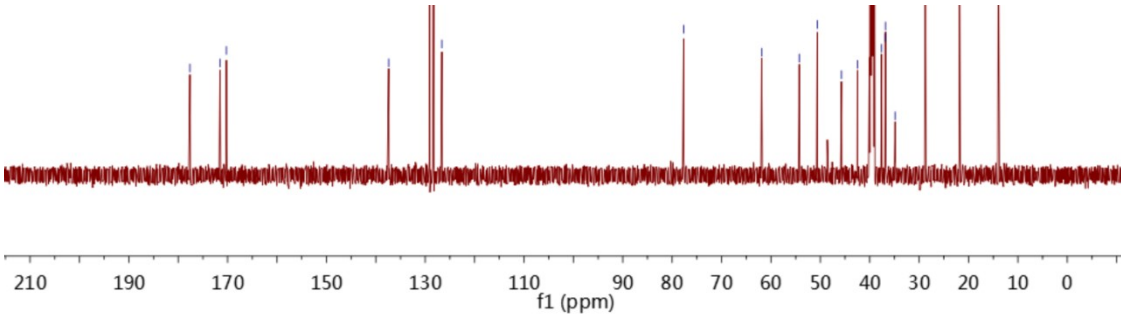
^{1}H NMR (Natural Product, 600 MHz, DMSO-d_6)



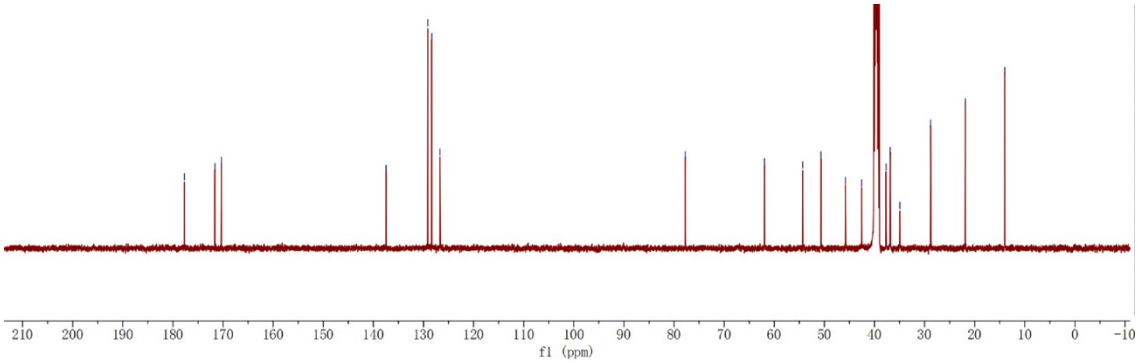
^{1}H NMR (Synthetic Product, 500 MHz, DMSO-d_6)



^{13}C NMR (Natural Product, 150 MHz, DMSO-d_6)

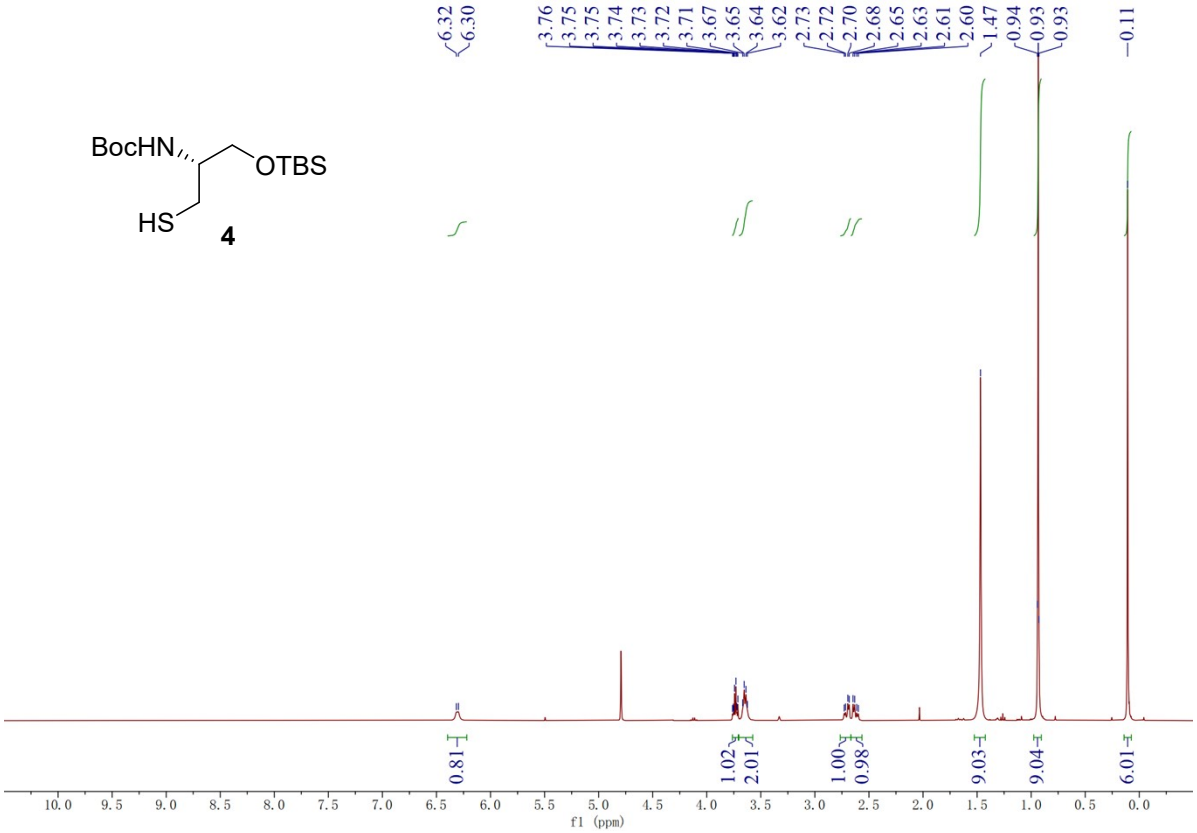


^{13}C NMR (Synthetic Product, 126 MHz, DMSO-d_6)

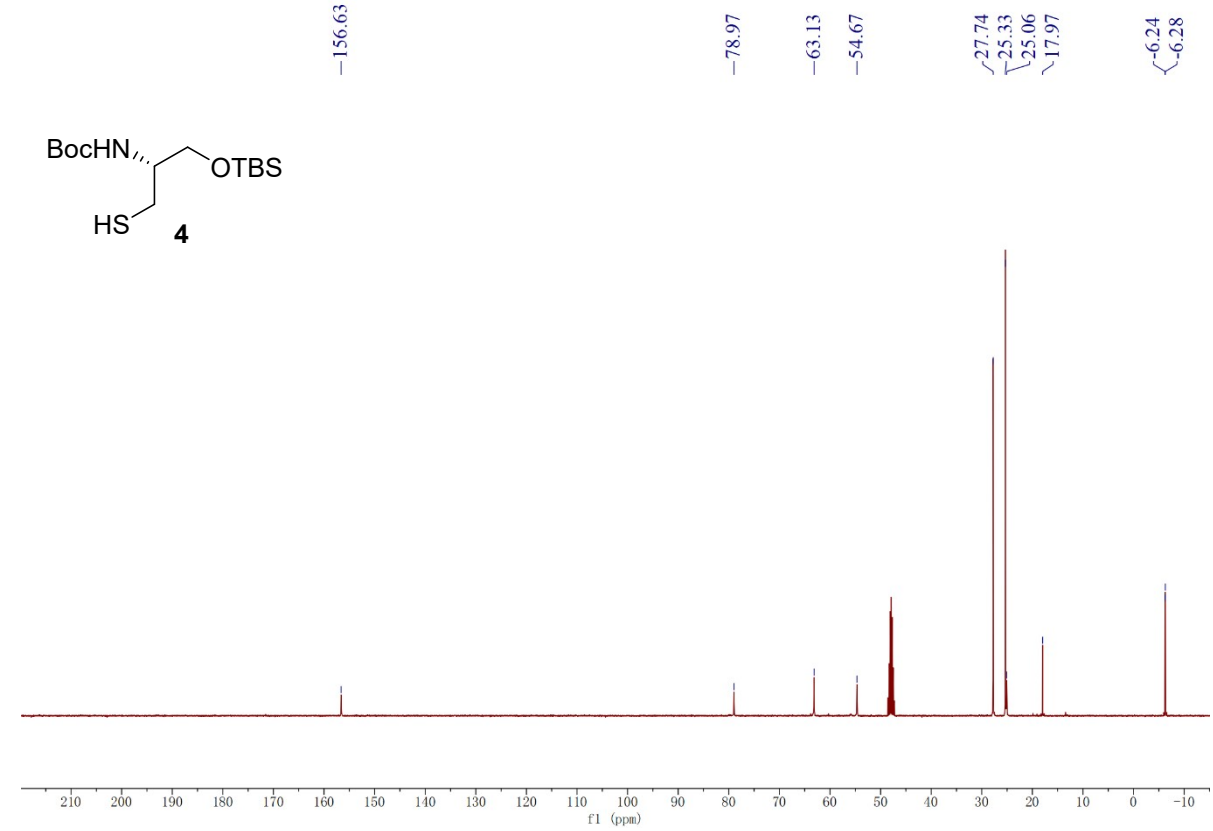


V. ^{1}H and ^{13}C NMR Spectra

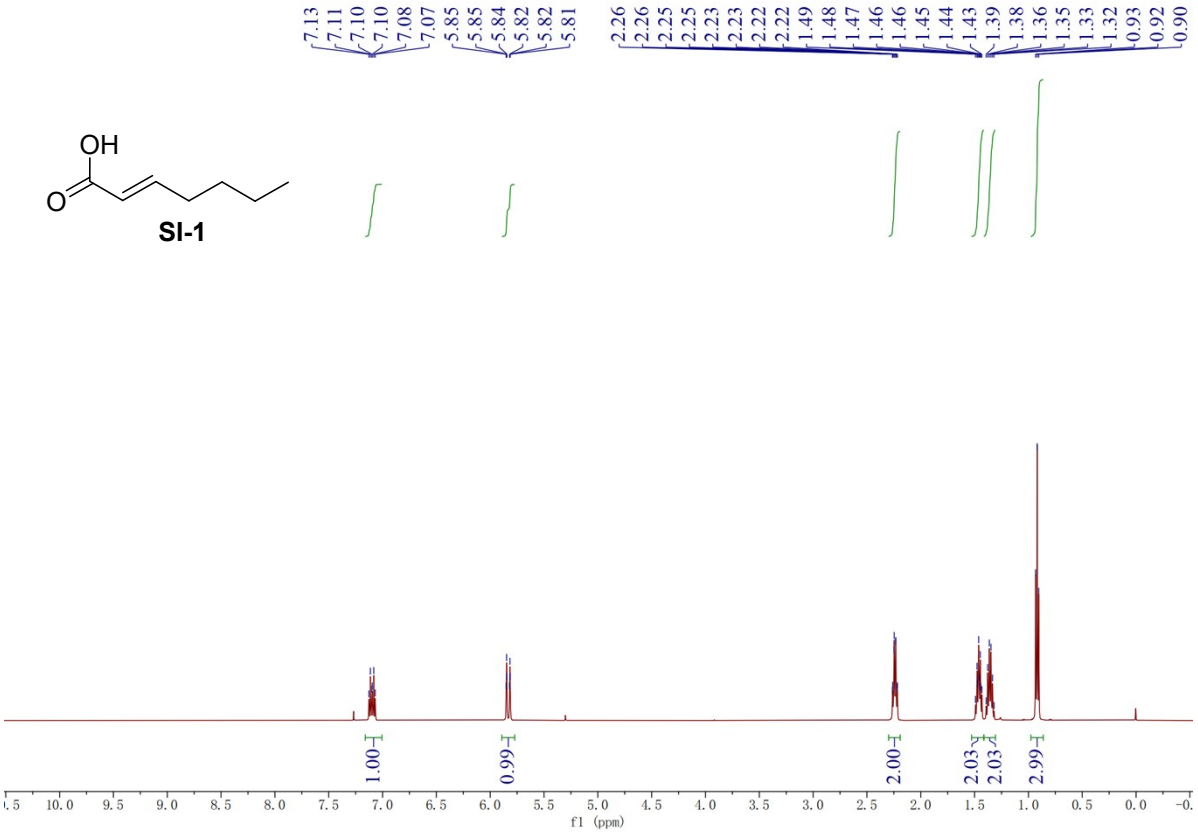
^{1}H NMR ($CDOD_3$, 400 MHz)



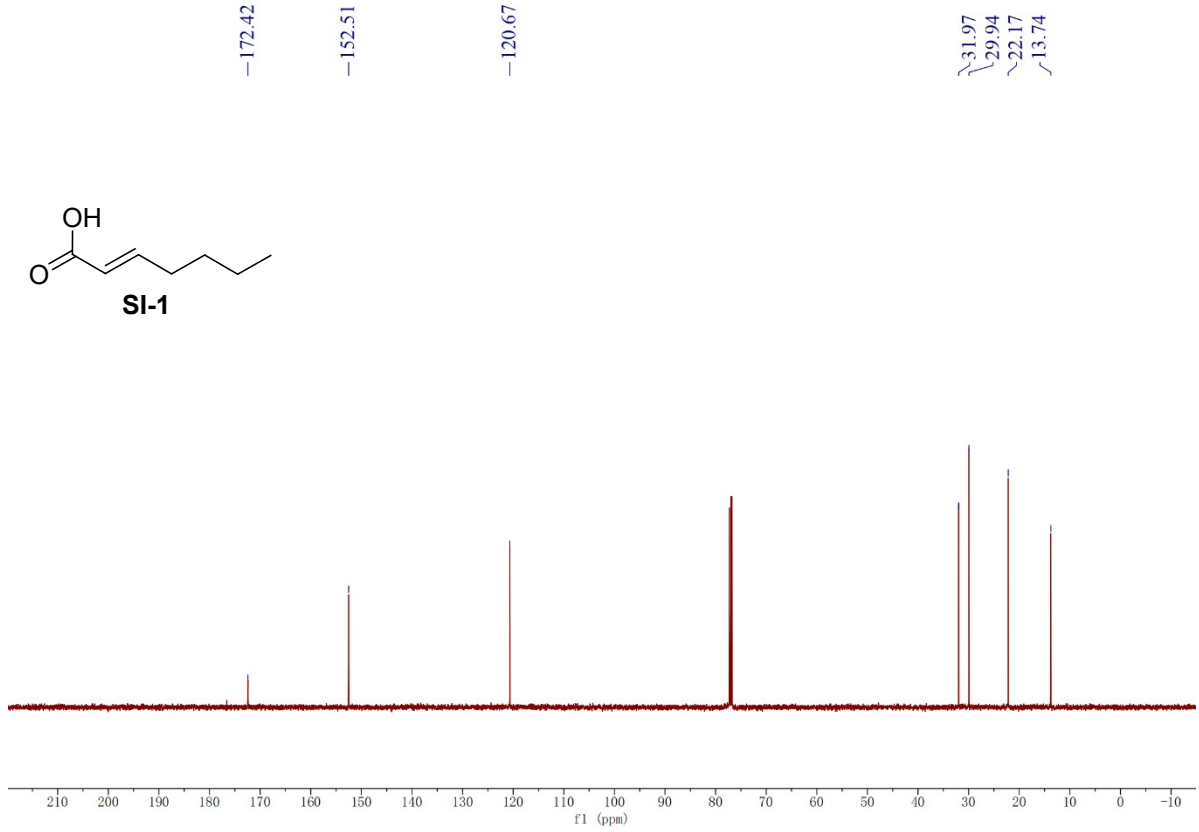
^{13}C NMR ($CDOD_3$, 101 MHz)



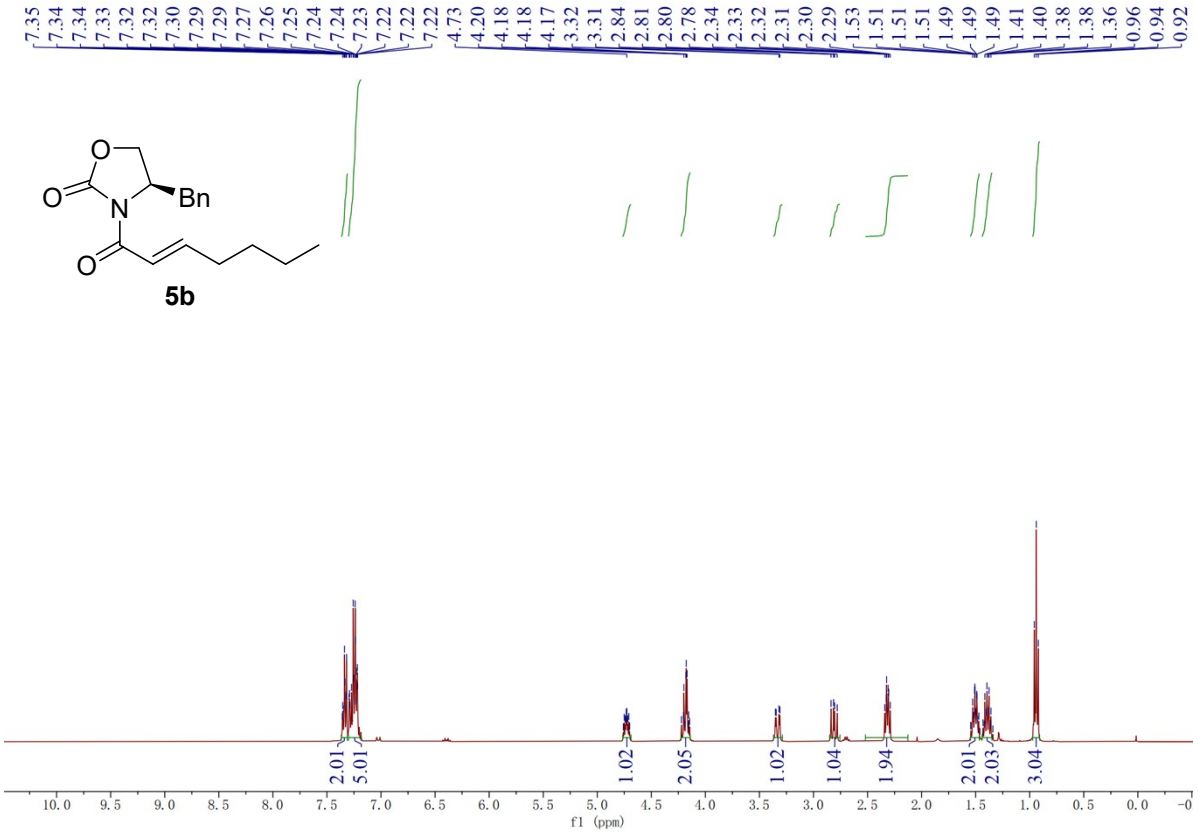
^{1}H NMR ($CDCl_3$, 500 MHz)



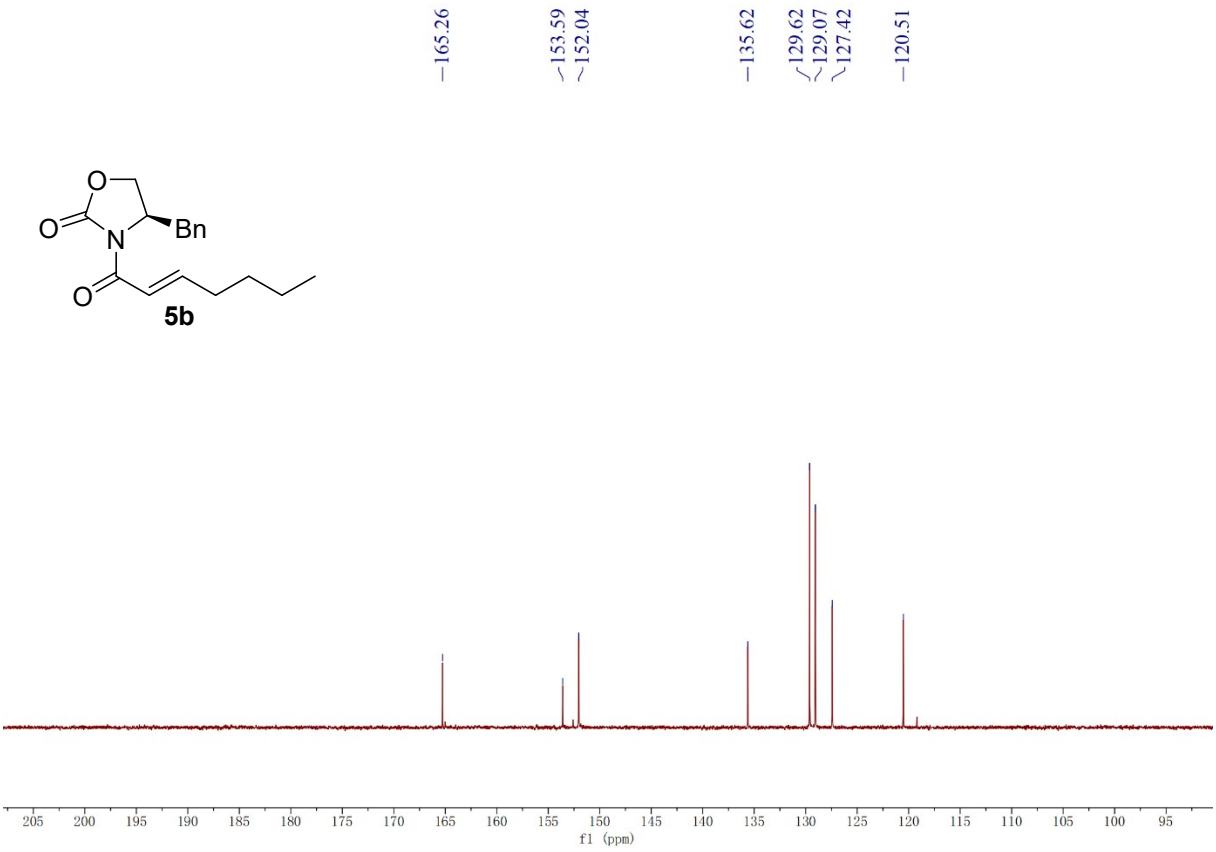
^{13}C NMR ($CDCl_3$, 126 MHz)



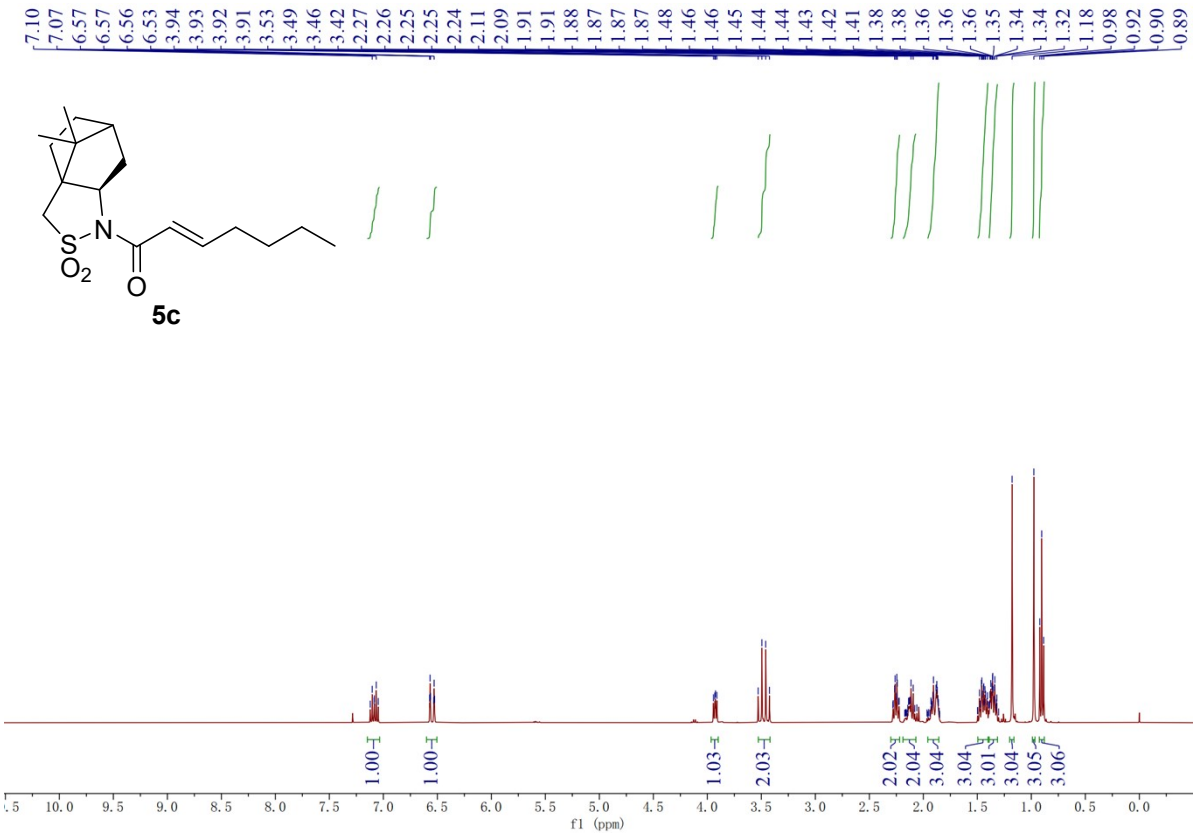
^{1}H NMR ($CDCl_3$, 400 MHz)



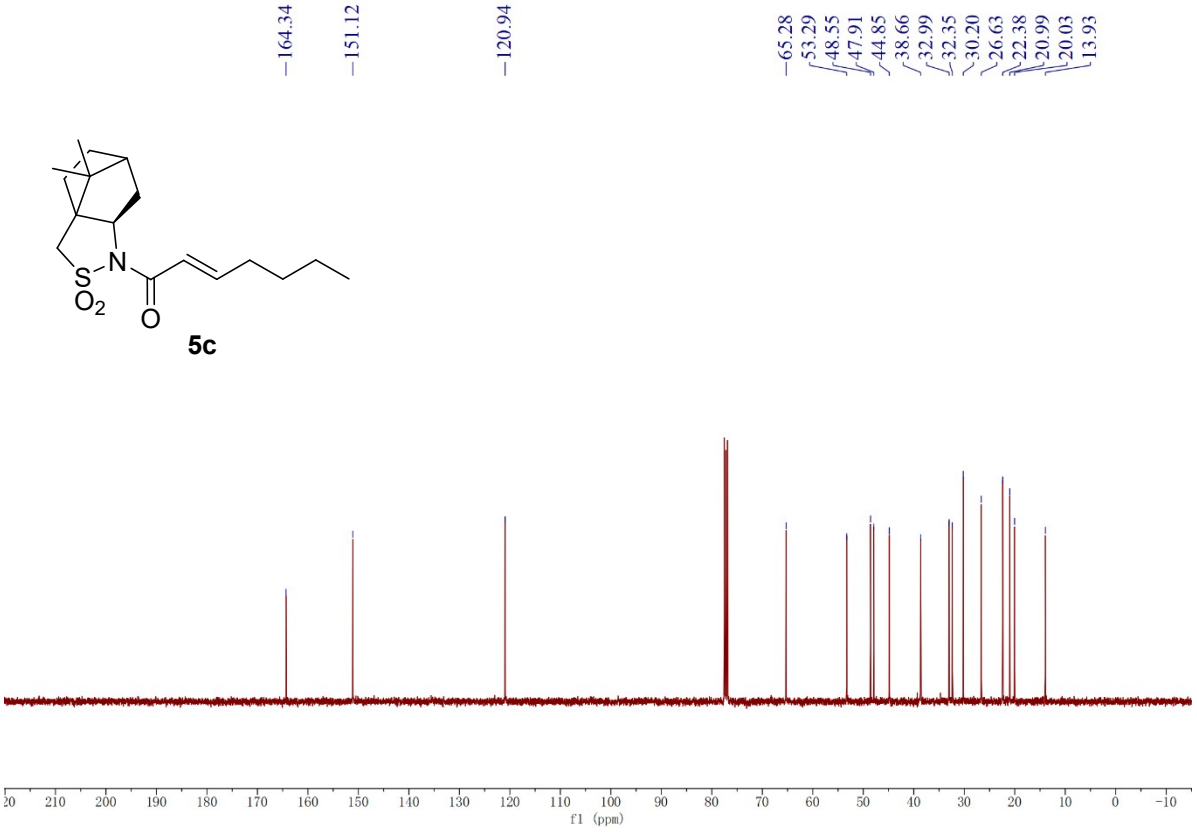
^{13}C NMR ($CDCl_3$, 101 MHz)



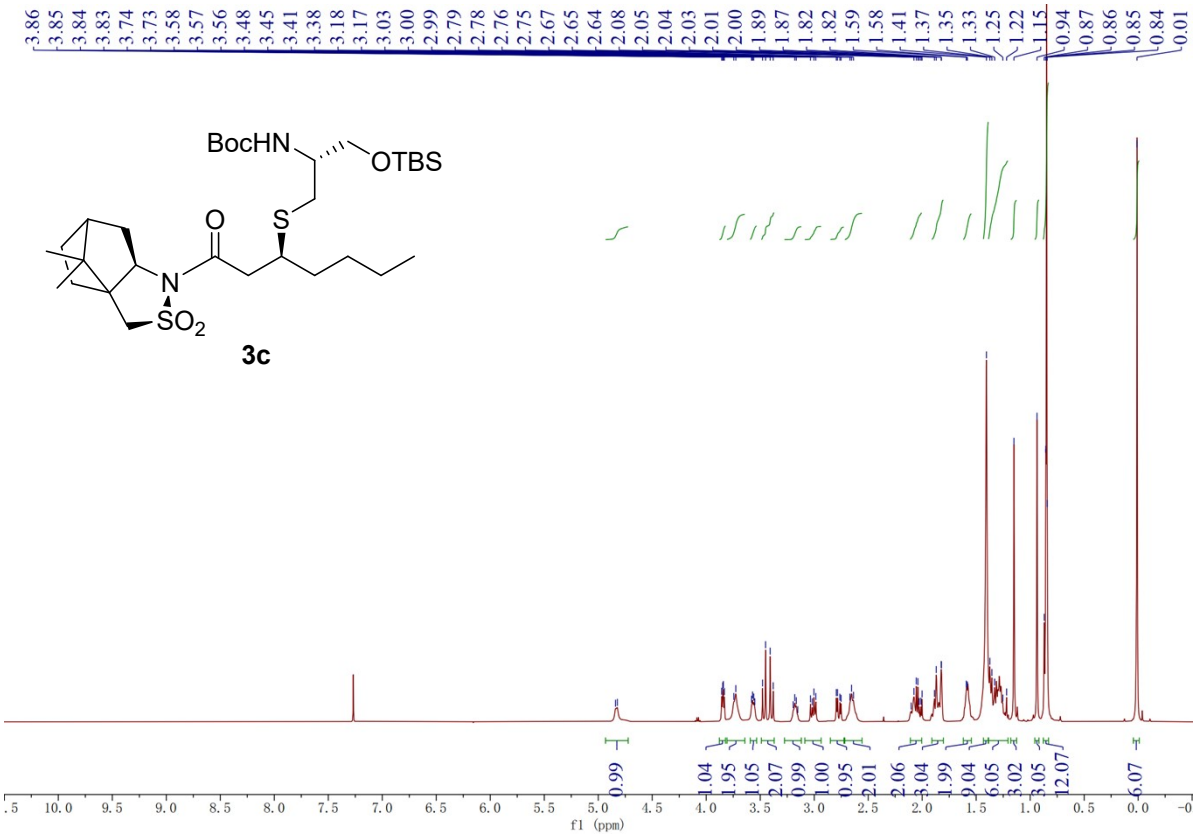
^{1}H NMR ($CDCl_3$, 400 MHz)



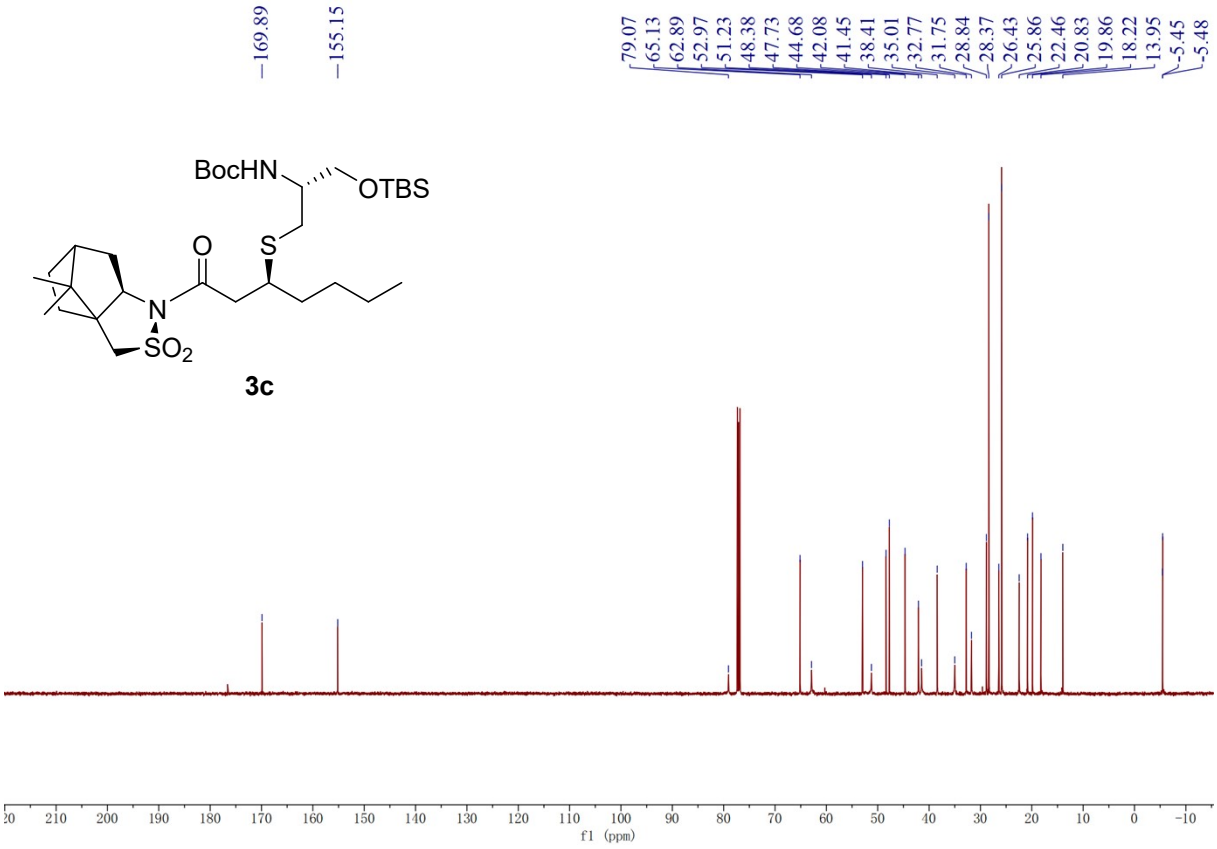
^{13}C NMR ($CDCl_3$, 101 MHz)



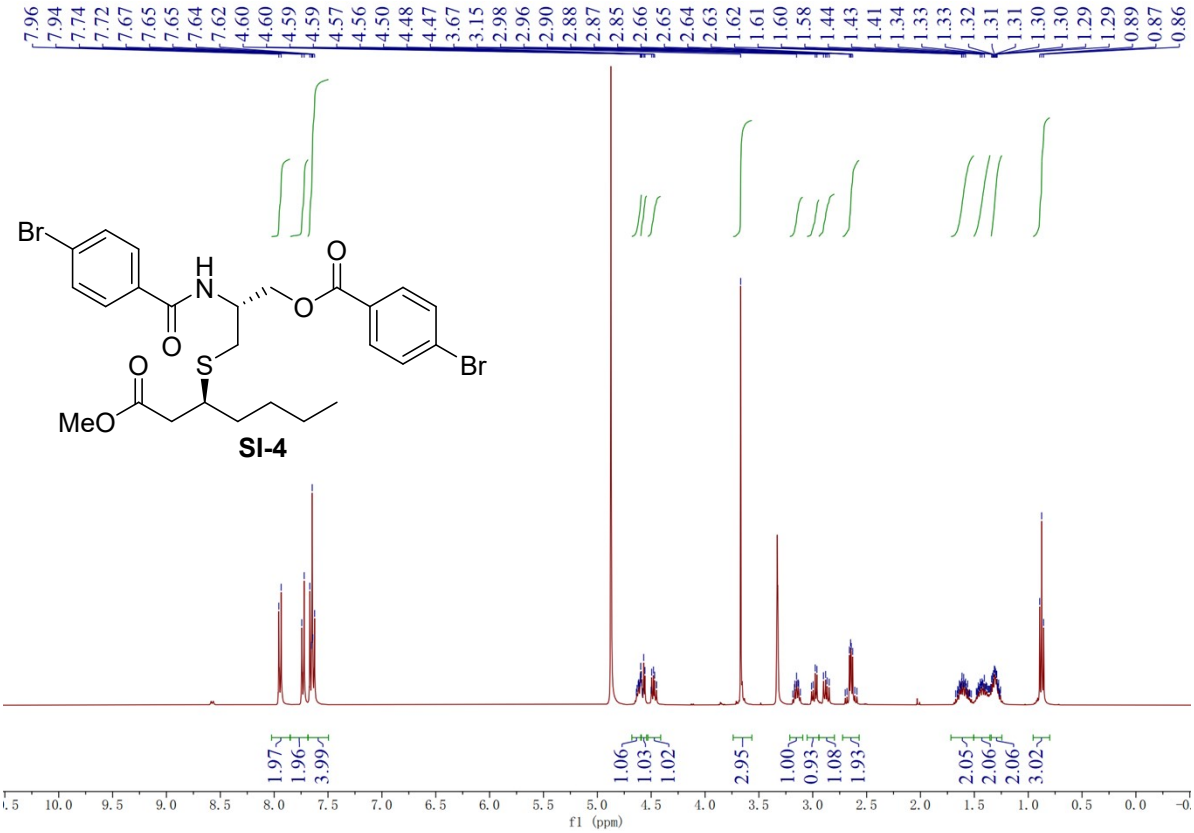
^{1}H NMR ($CDCl_3$, 500 MHz)



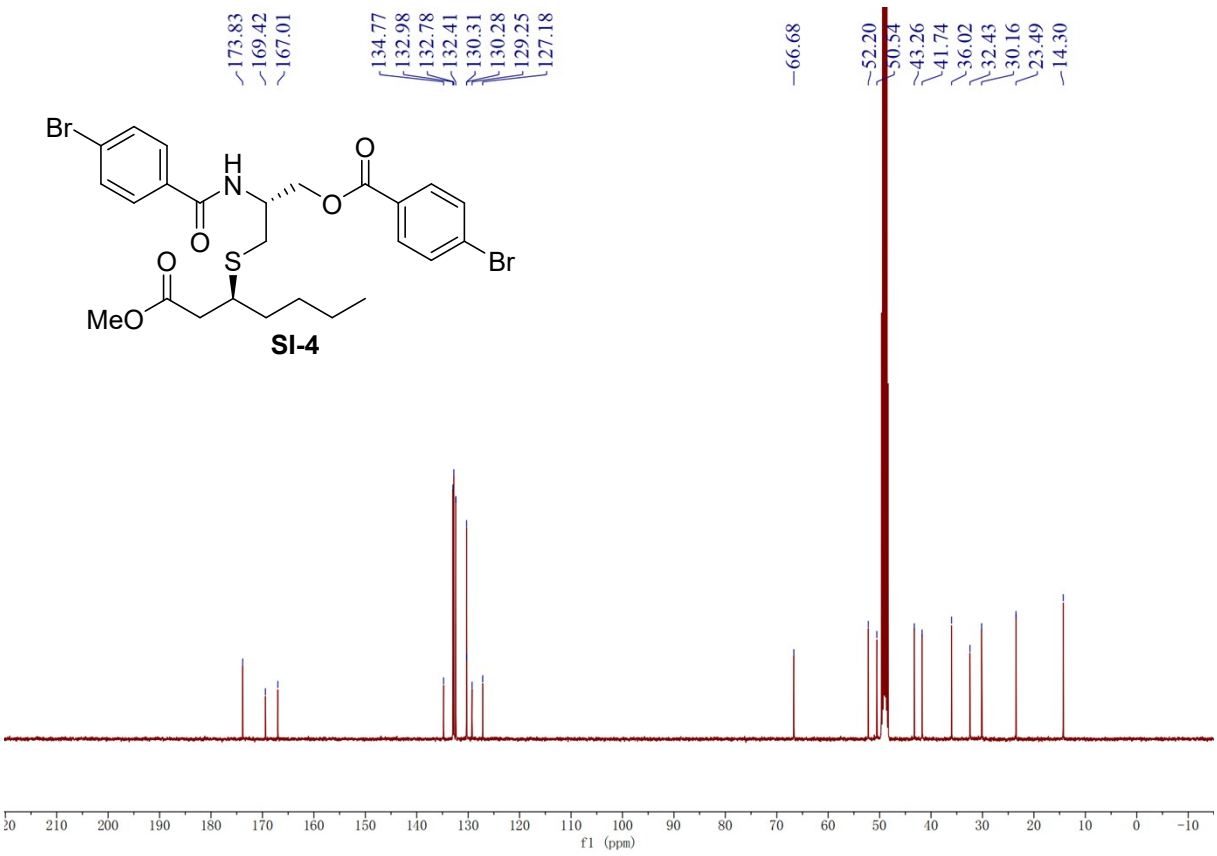
^{13}C NMR ($CDCl_3$, 126 MHz)



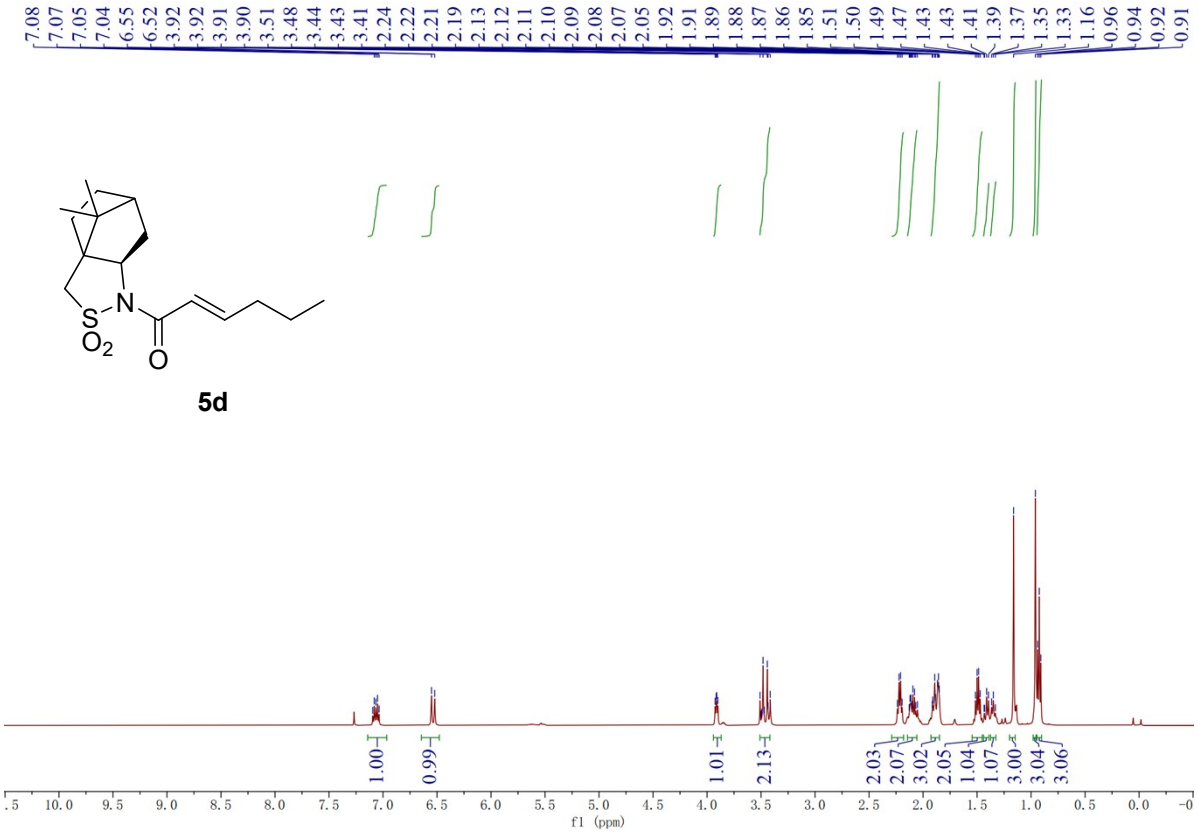
^{1}H NMR (CD_3OD, 400 MHz)



^{13}C NMR (CD_3OD, 101 MHz)

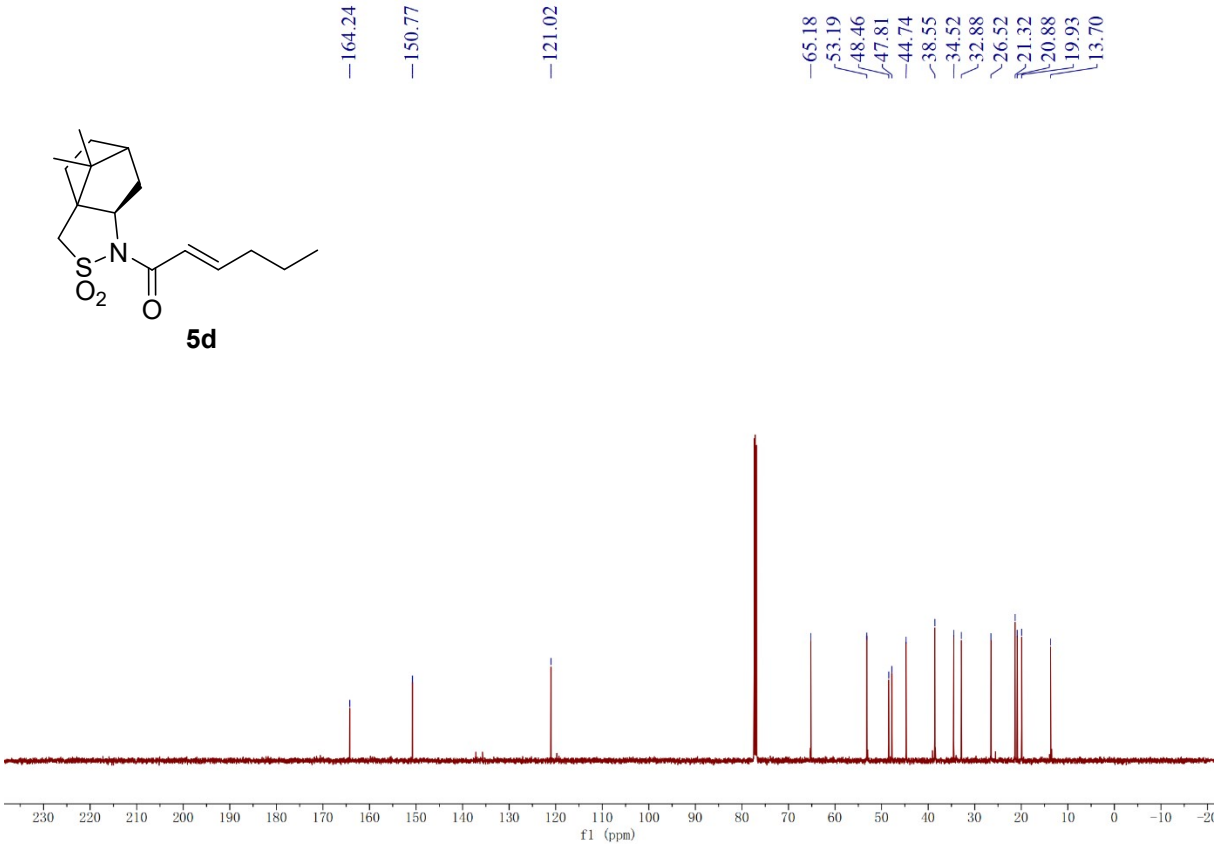


^{1}H NMR ($CDCl_3$, 500 MHz)



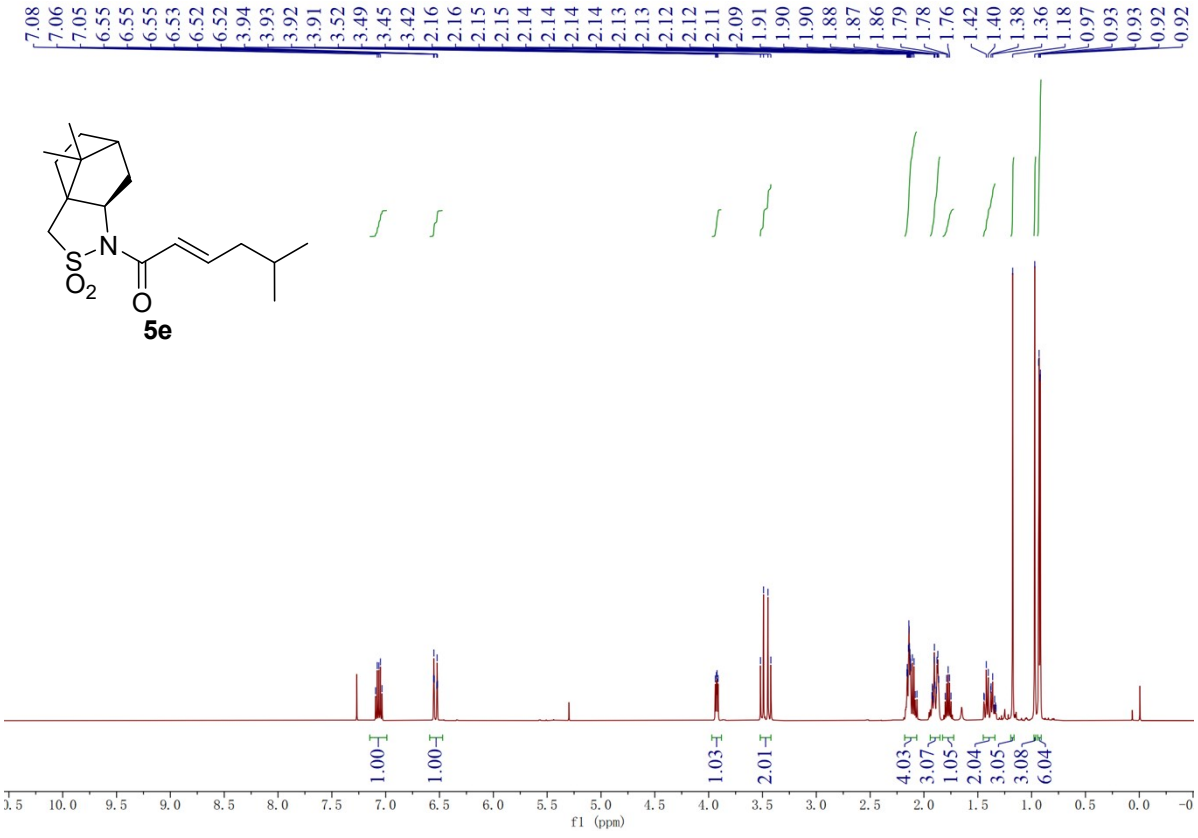
5d

^{13}C NMR ($CDCl_3$, 126 MHz)



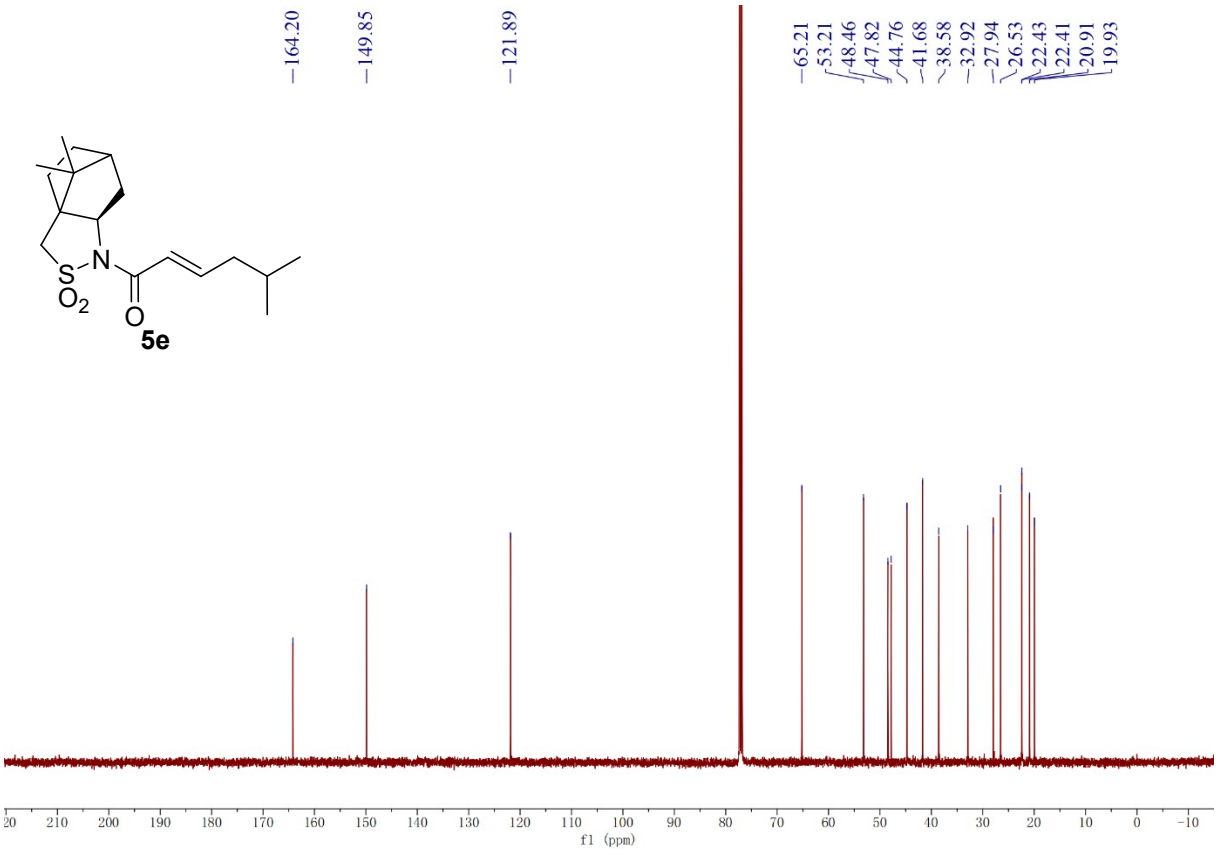
5d

^{1}H NMR ($CDCl_3$, 500 MHz)



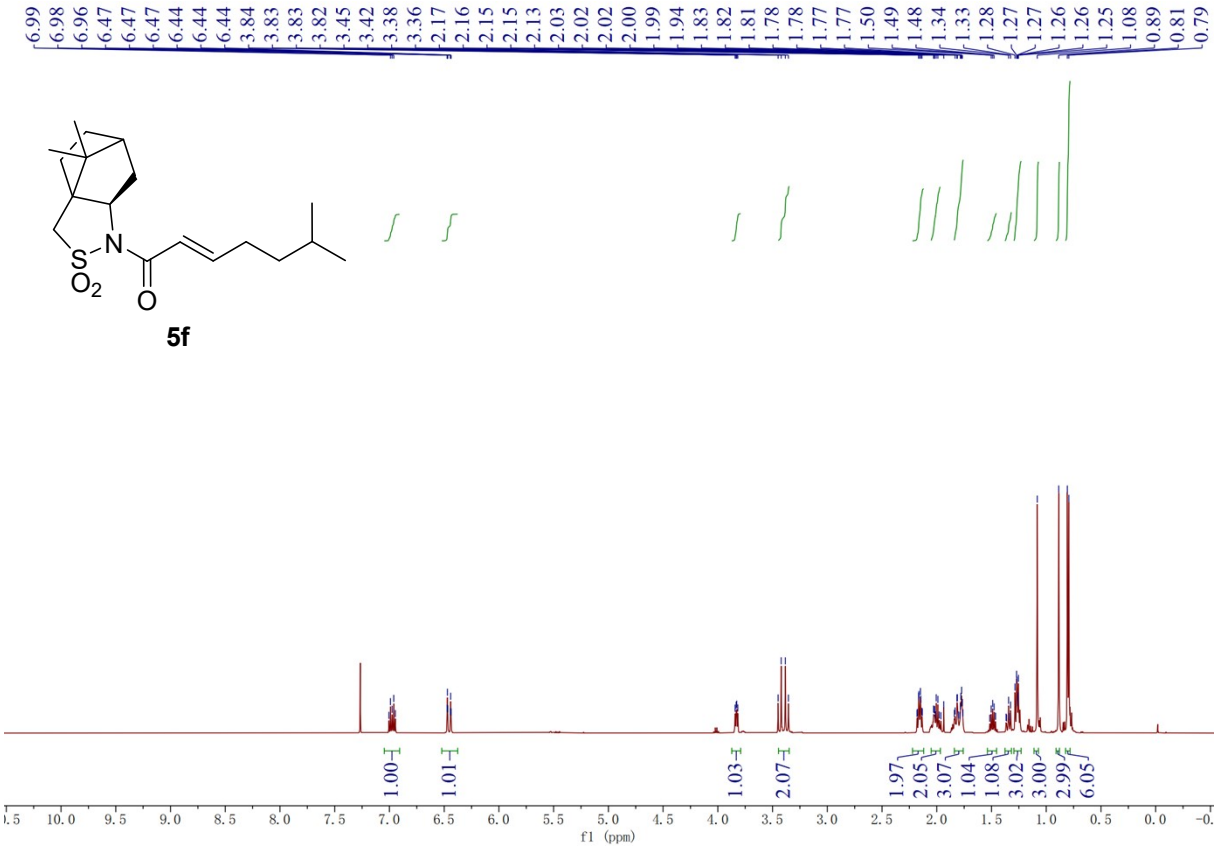
5e

^{13}C NMR ($CDCl_3$, 126 MHz)



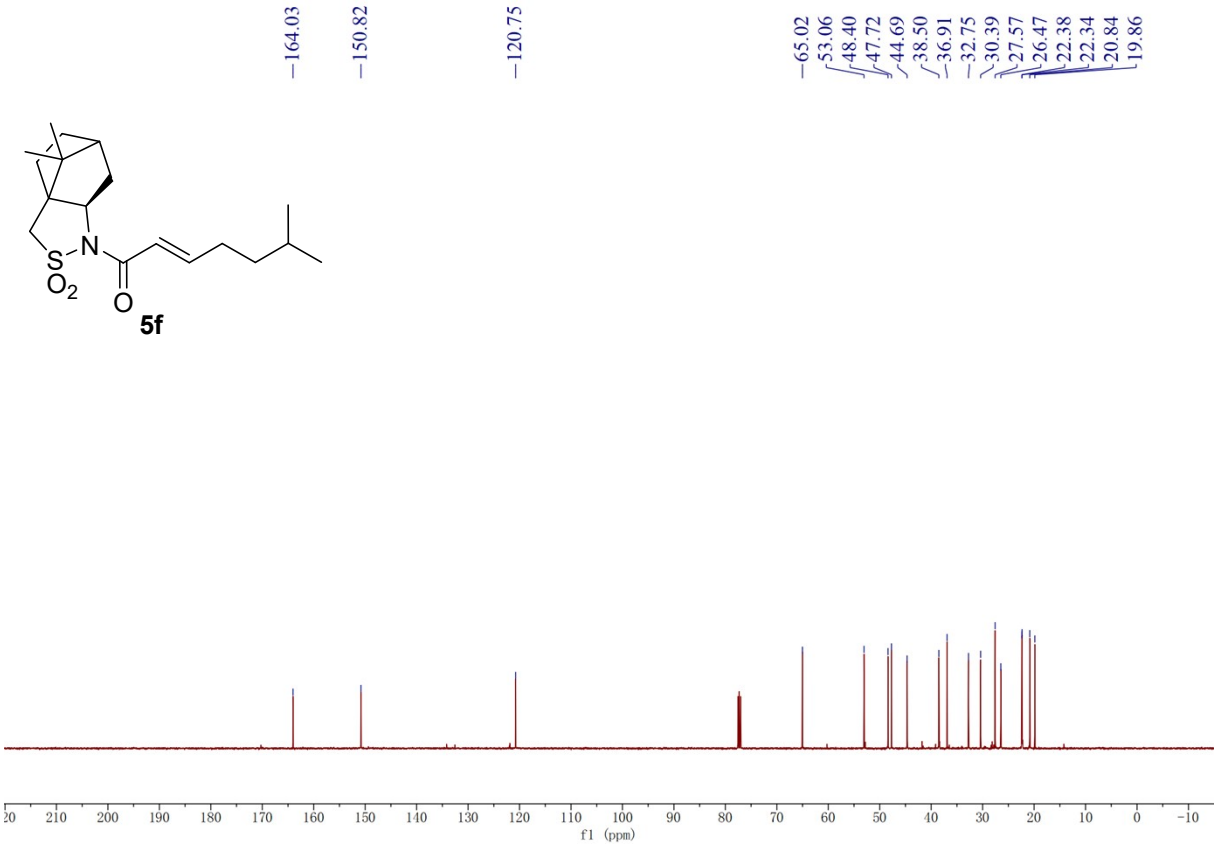
5e

^{1}H NMR ($CDCl_3$, 500 MHz)



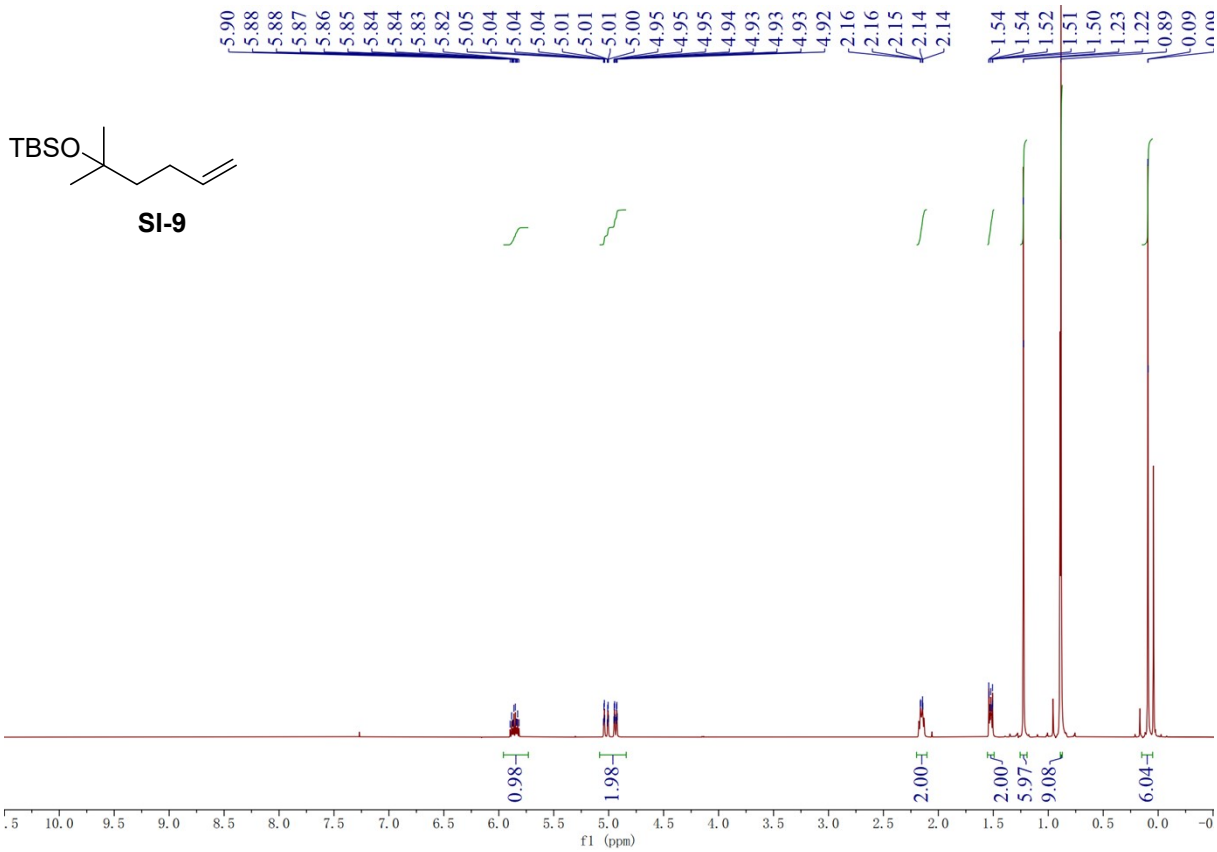
5f

^{13}C NMR ($CDCl_3$, 126 MHz)

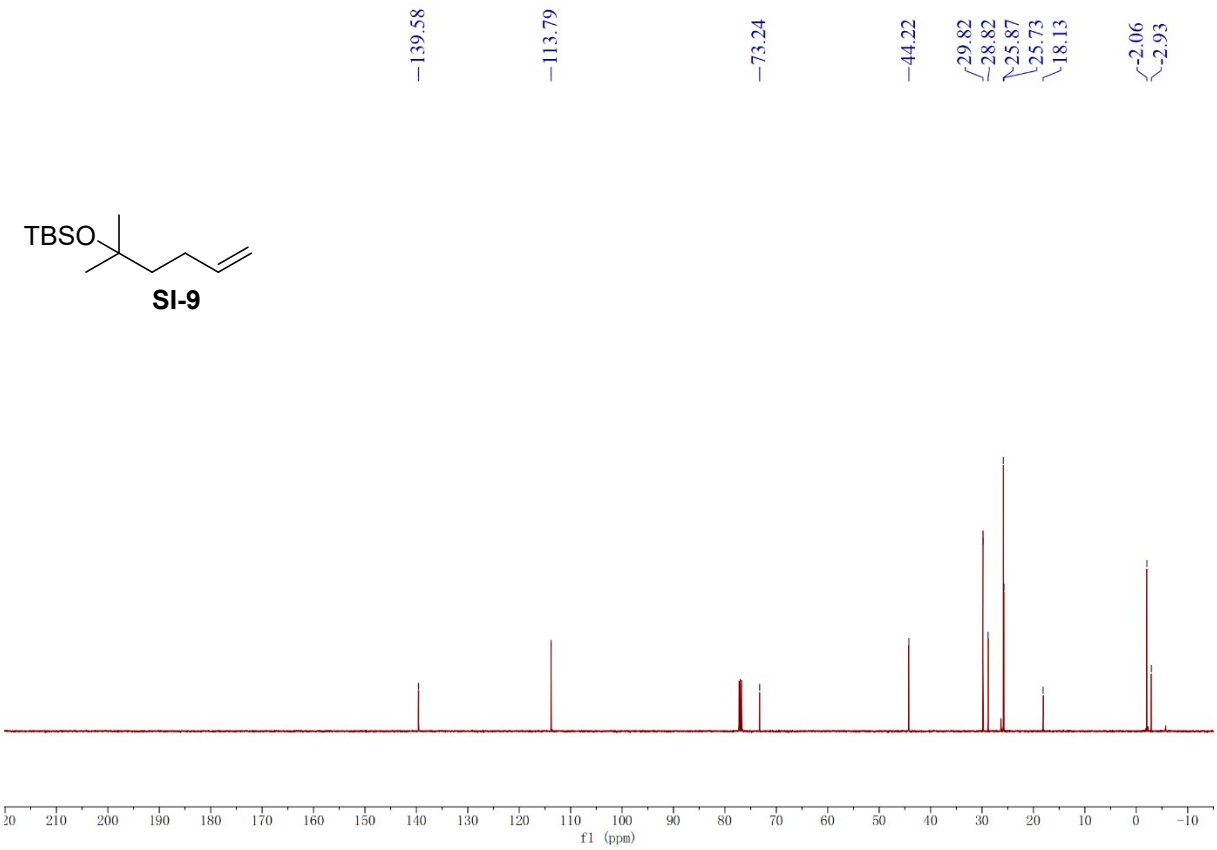


5f

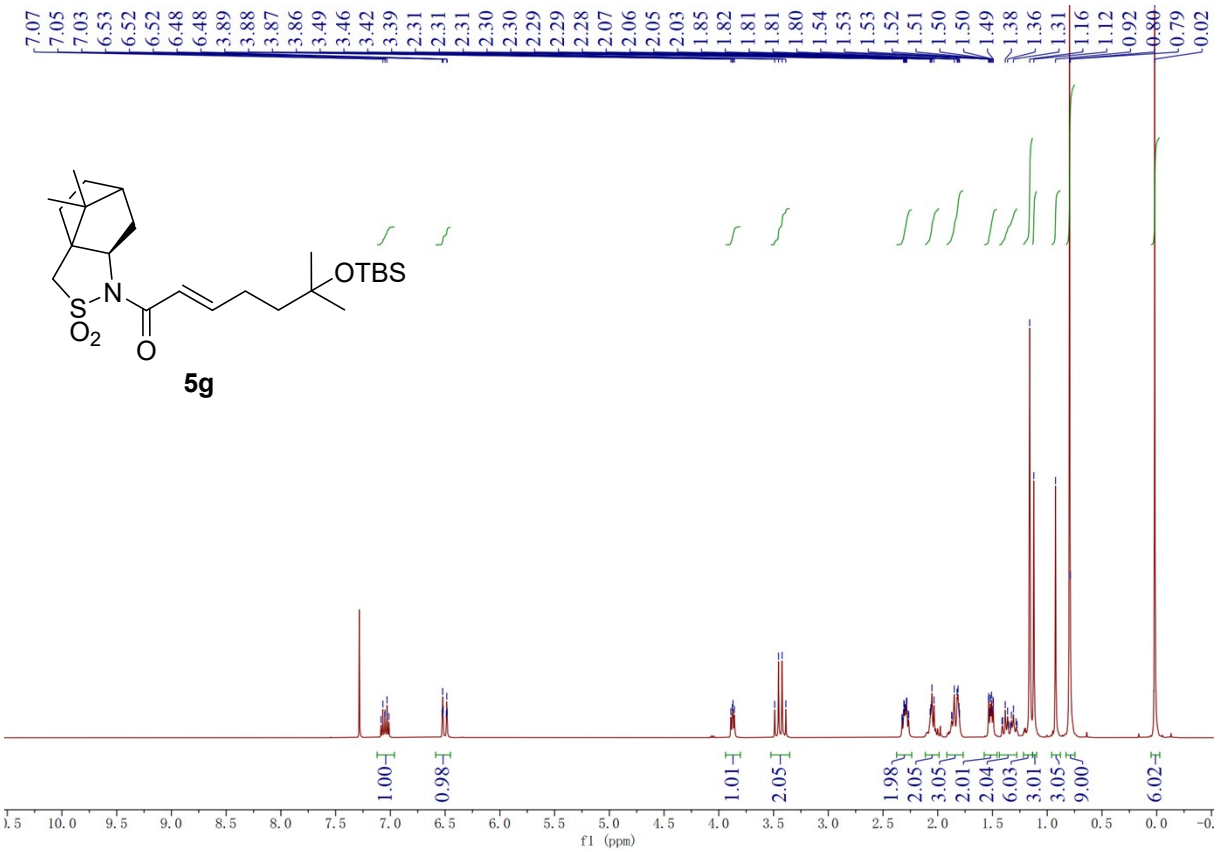
^{1}H NMR ($CDCl_3$, 400 MHz)



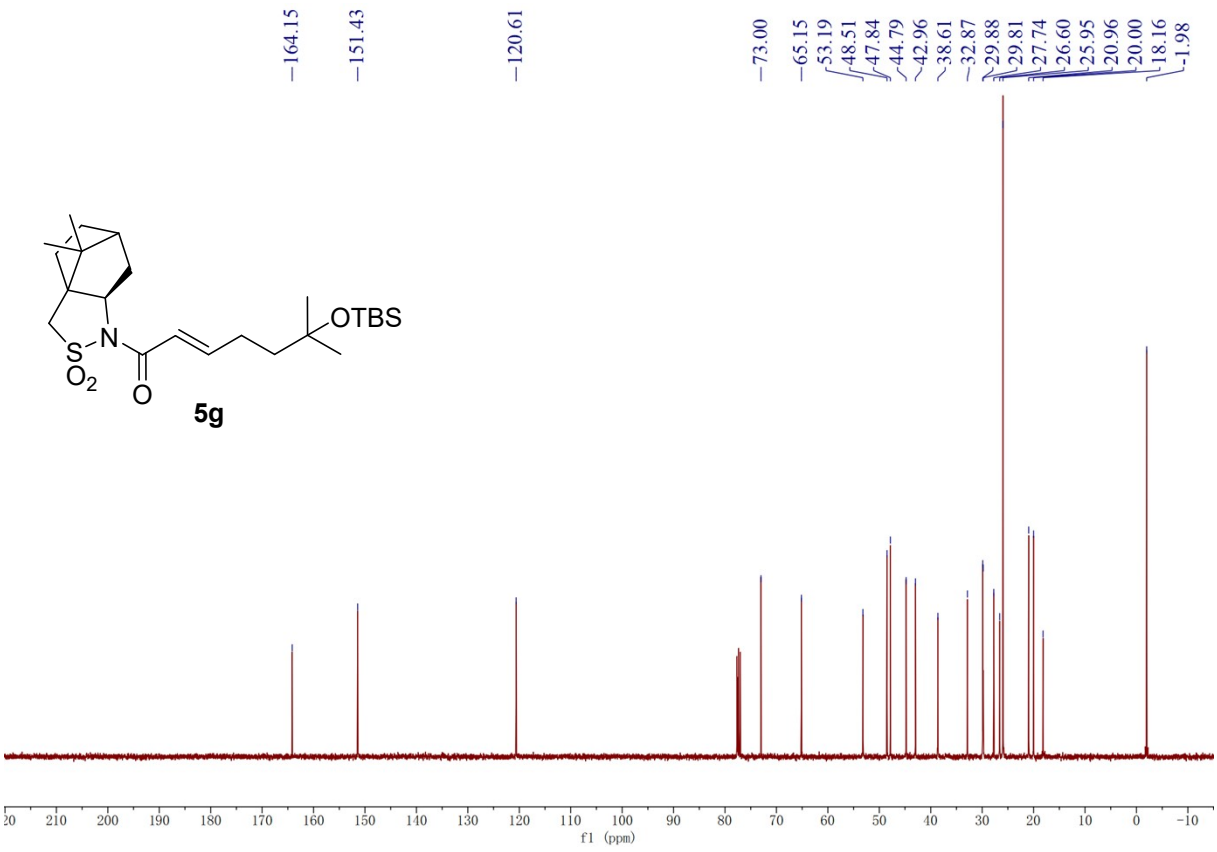
^{13}C NMR ($CDCl_3$, 101 MHz)



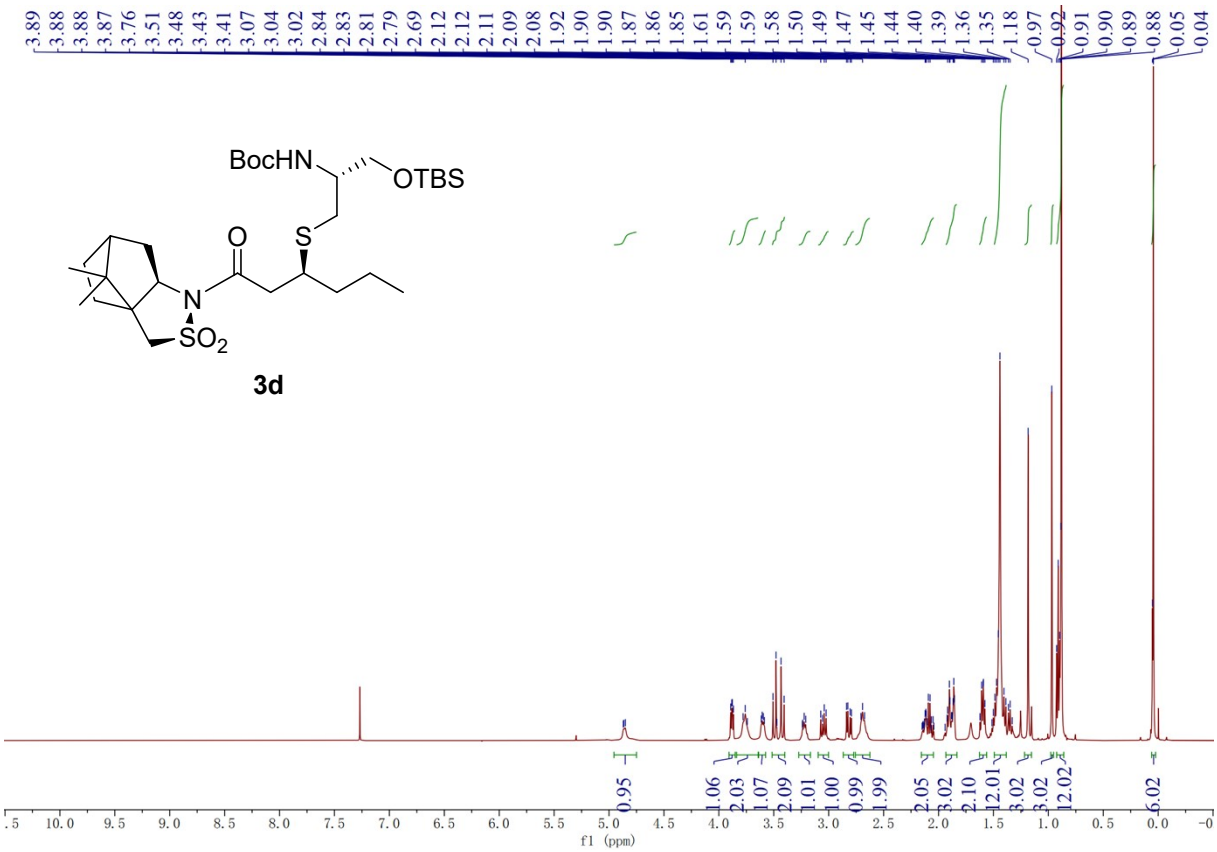
^{1}H NMR ($CDCl_3$, 500 MHz)



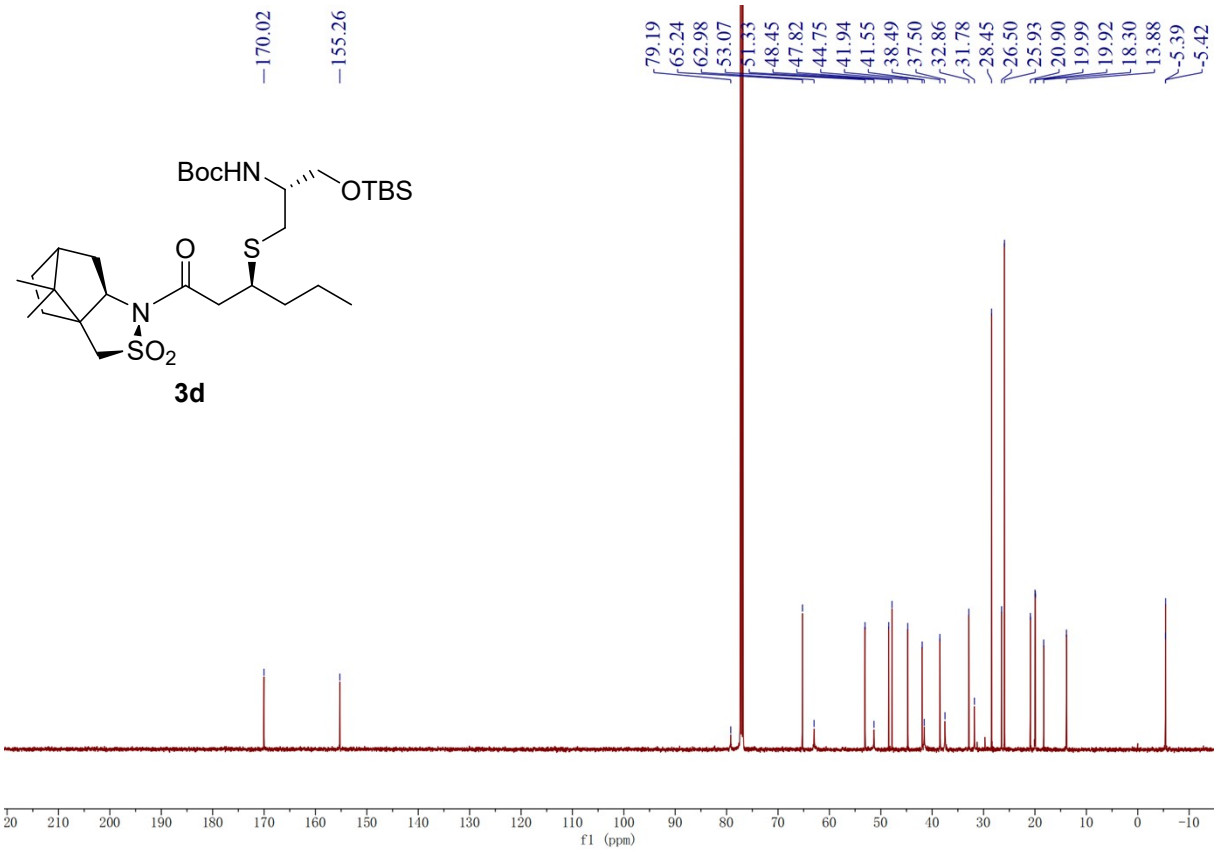
^{13}C NMR ($CDCl_3$, 126 MHz)



^{1}H NMR ($CDCl_3$, 500 MHz)



^{13}C NMR ($CDCl_3$, 126 MHz)



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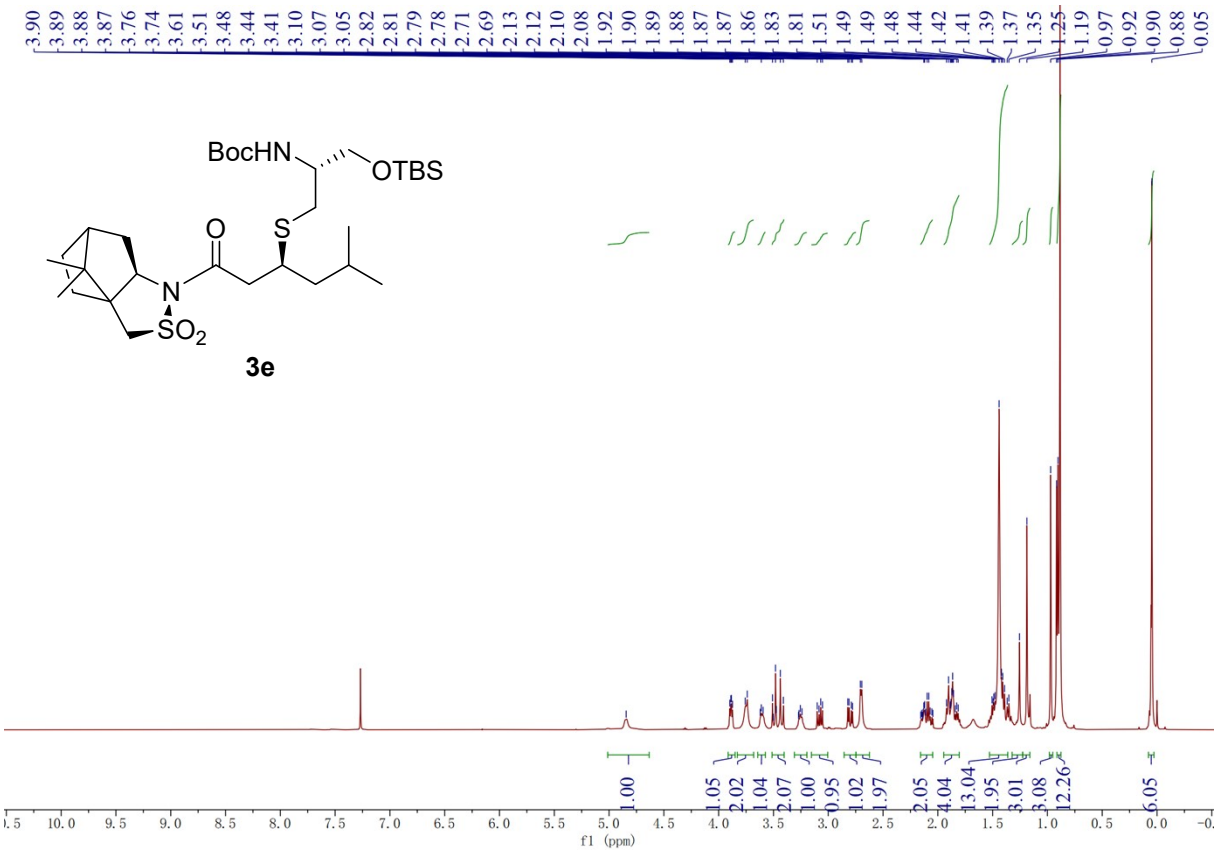
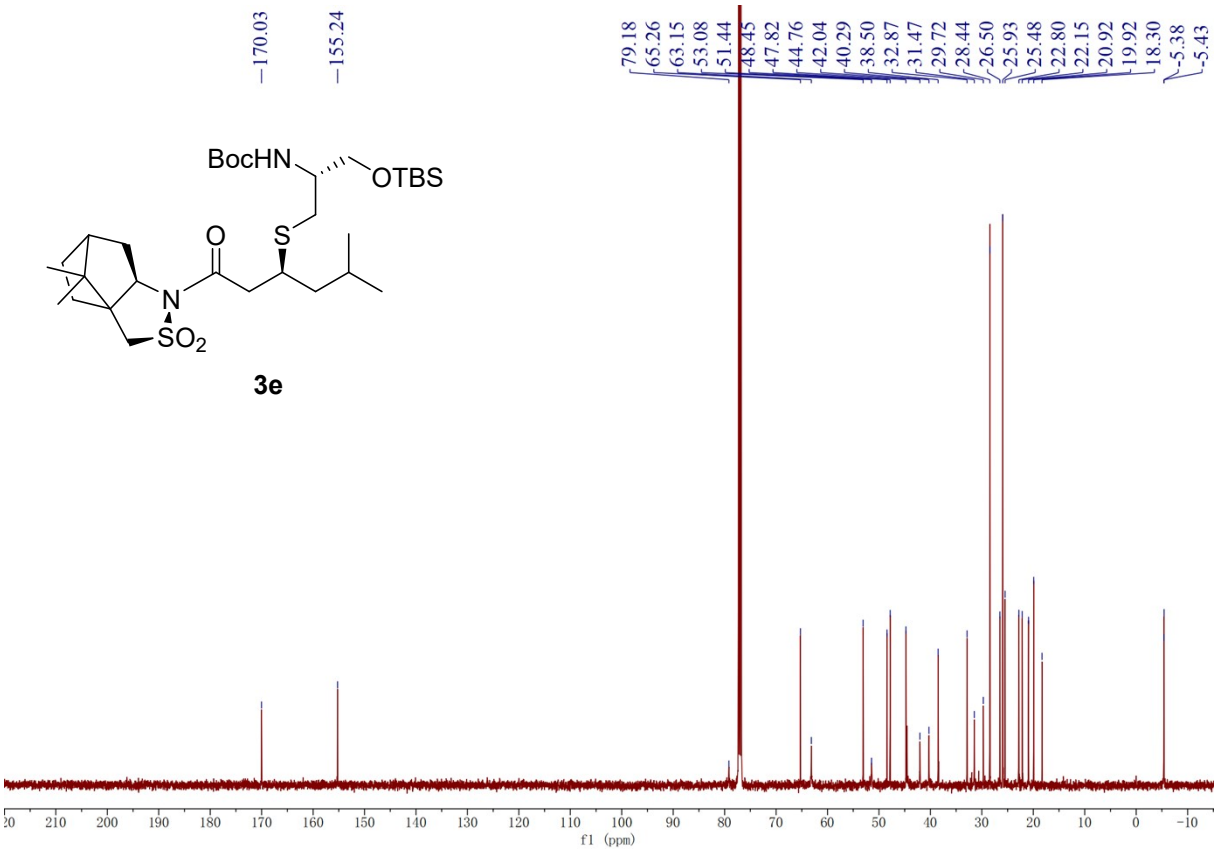
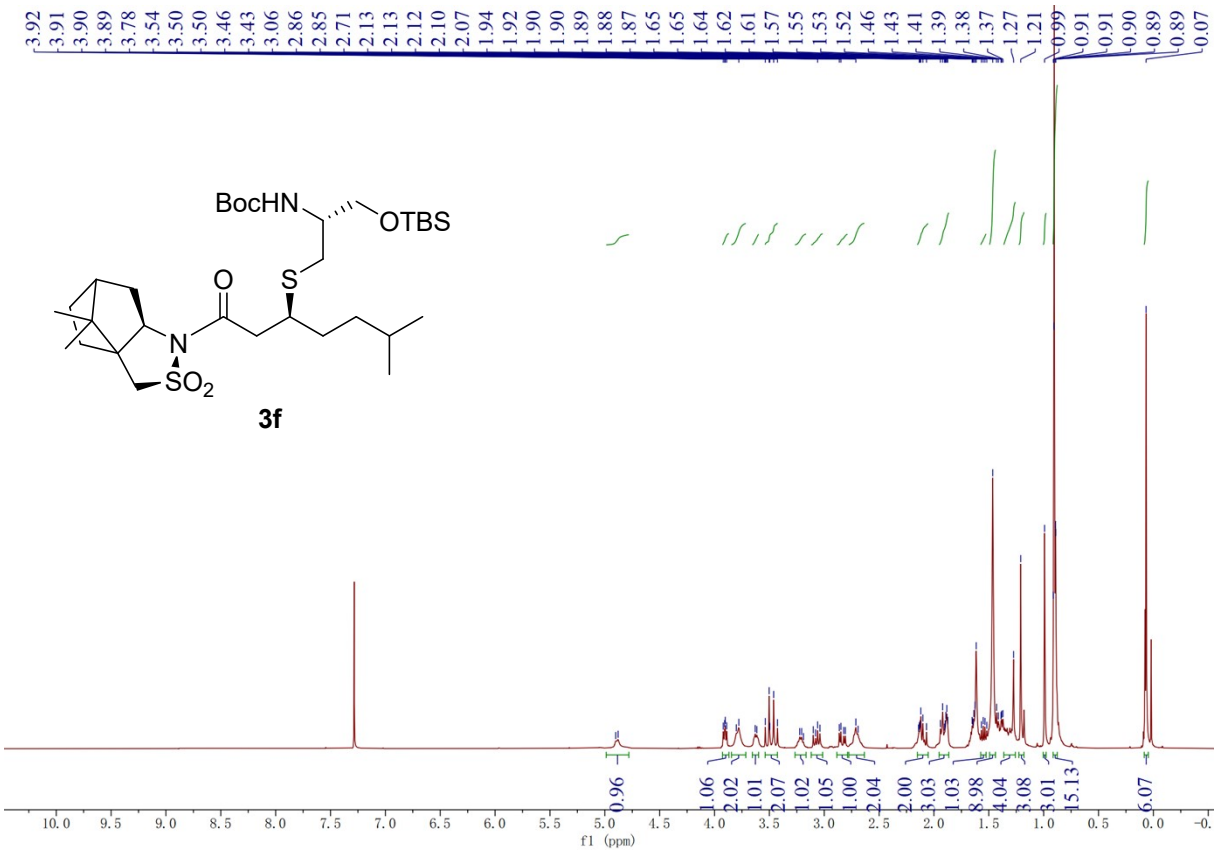


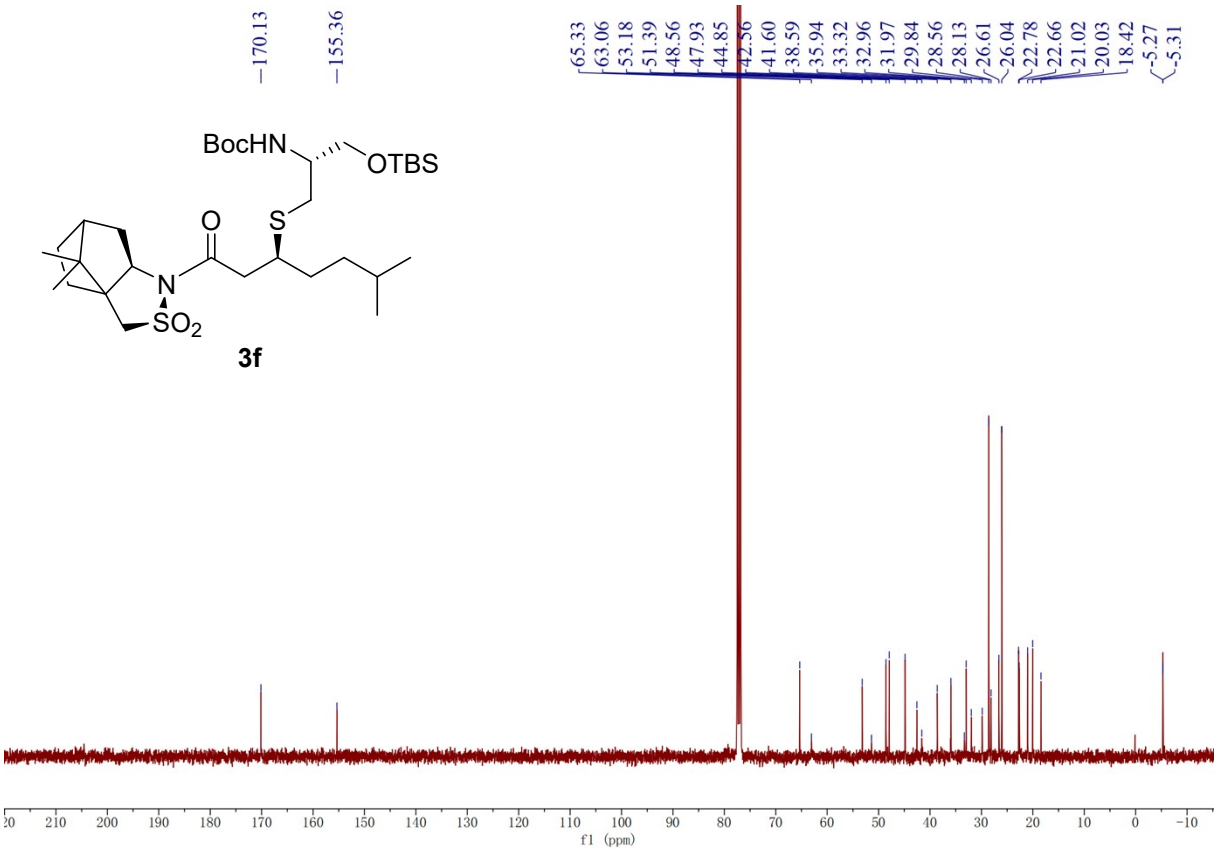
^{13}C NMR ($CDCl_3$, 126 MHz)



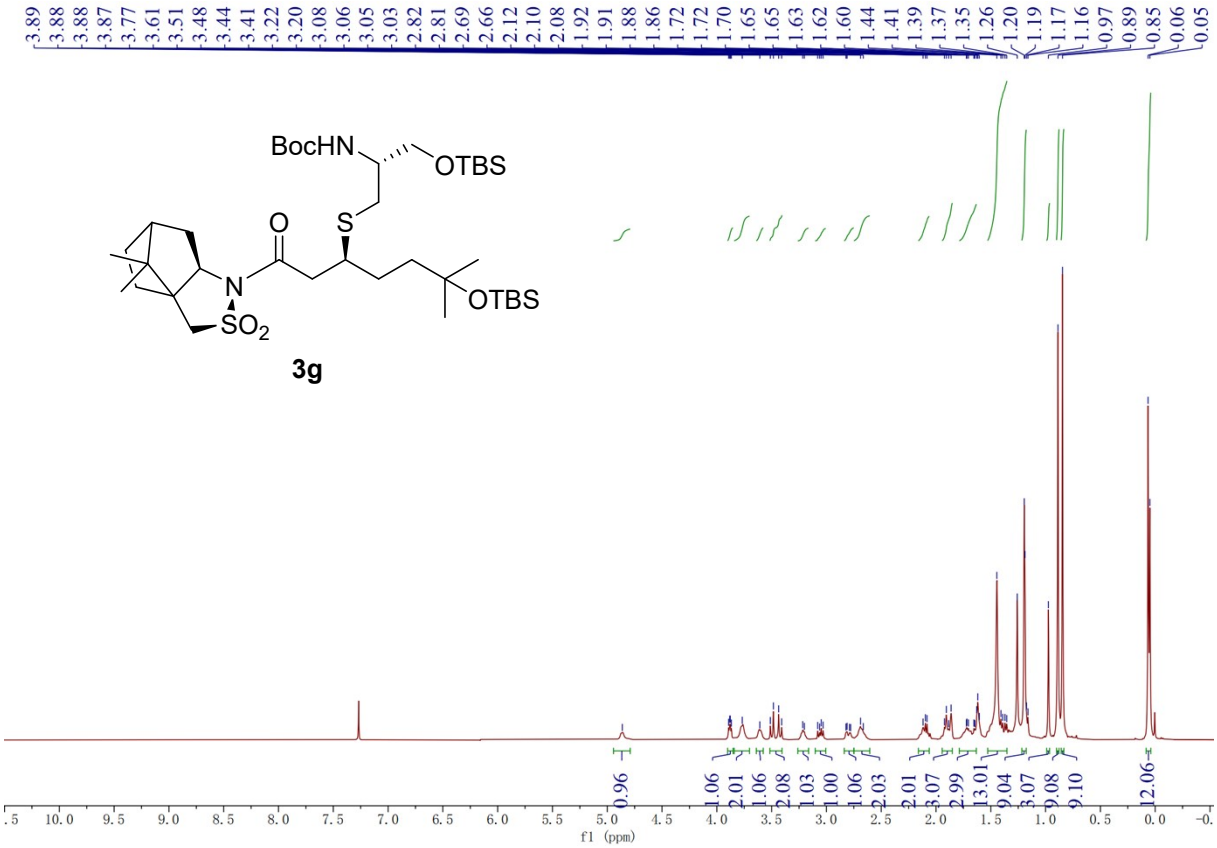
^{1}H NMR ($CDCl_3$, 400 MHz)



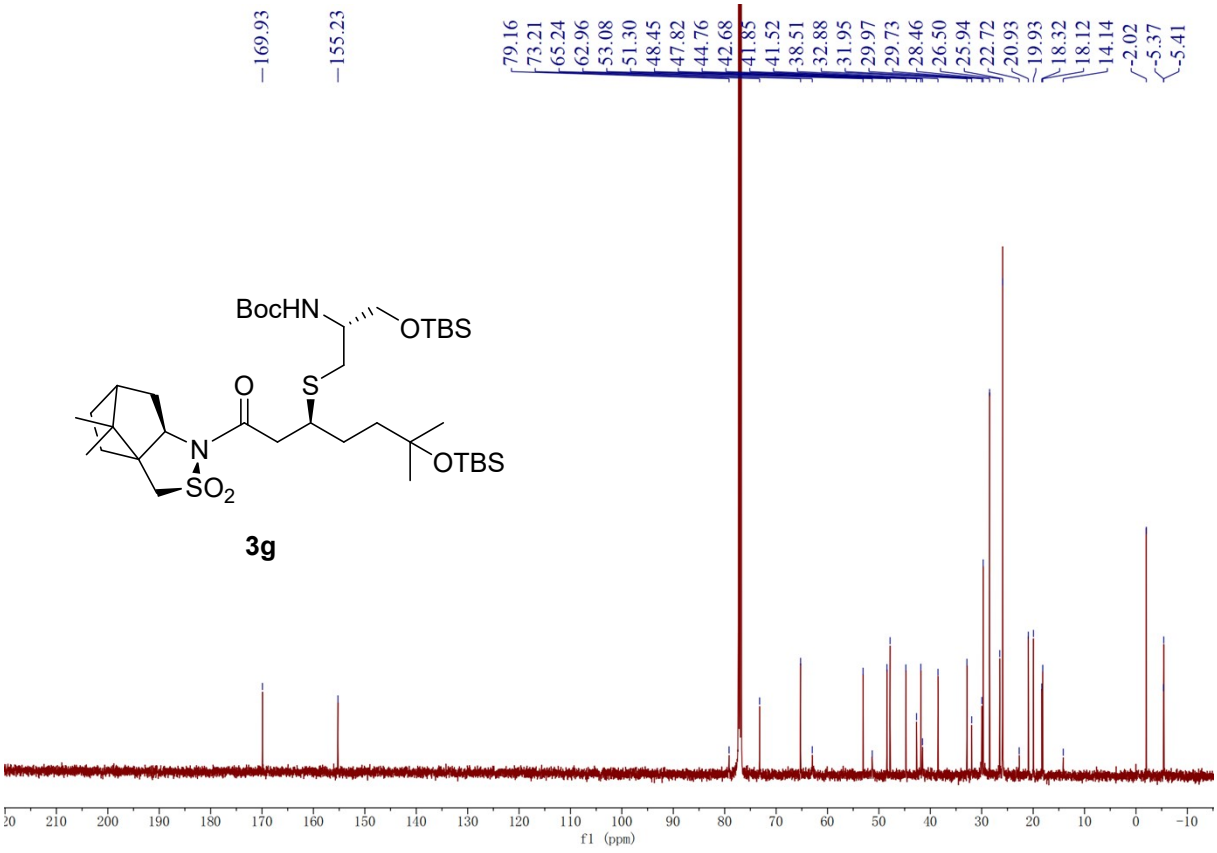
^{13}C NMR ($CDCl_3$, 101 MHz)



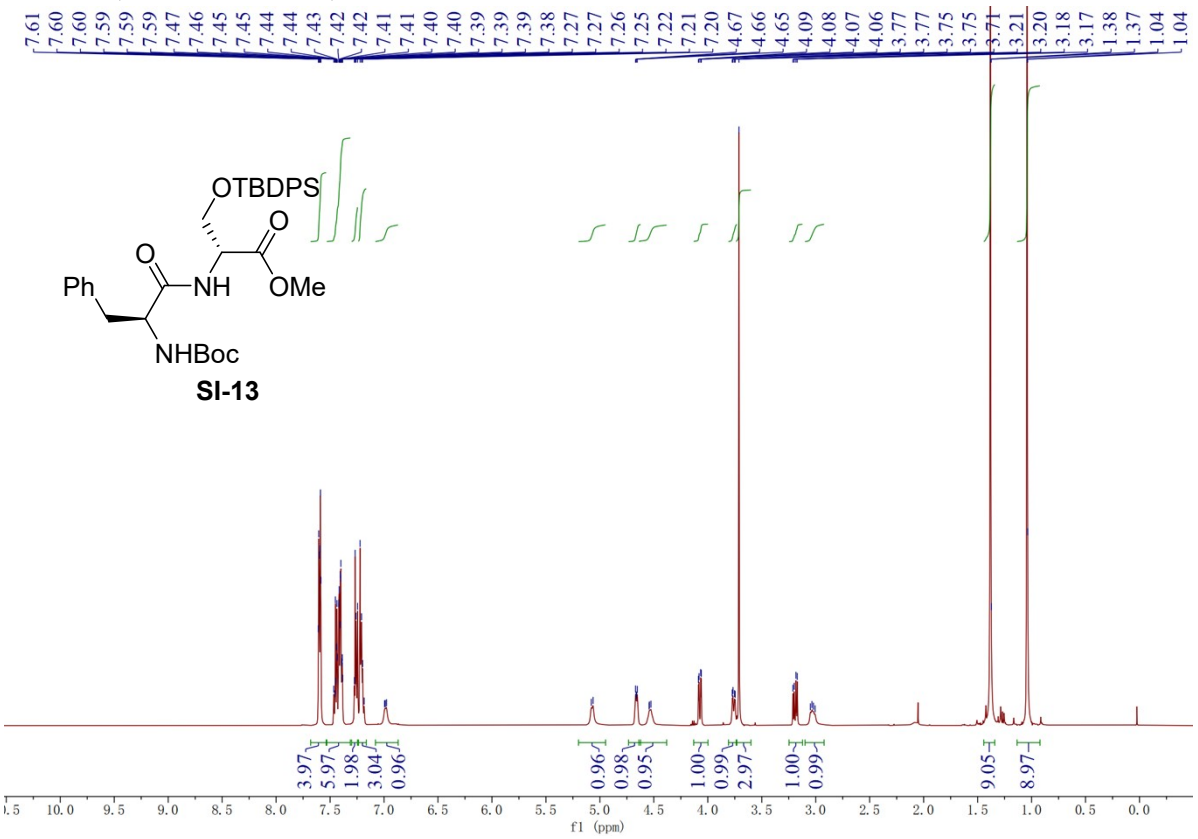
^{1}H NMR ($CDCl_3$, 500 MHz)



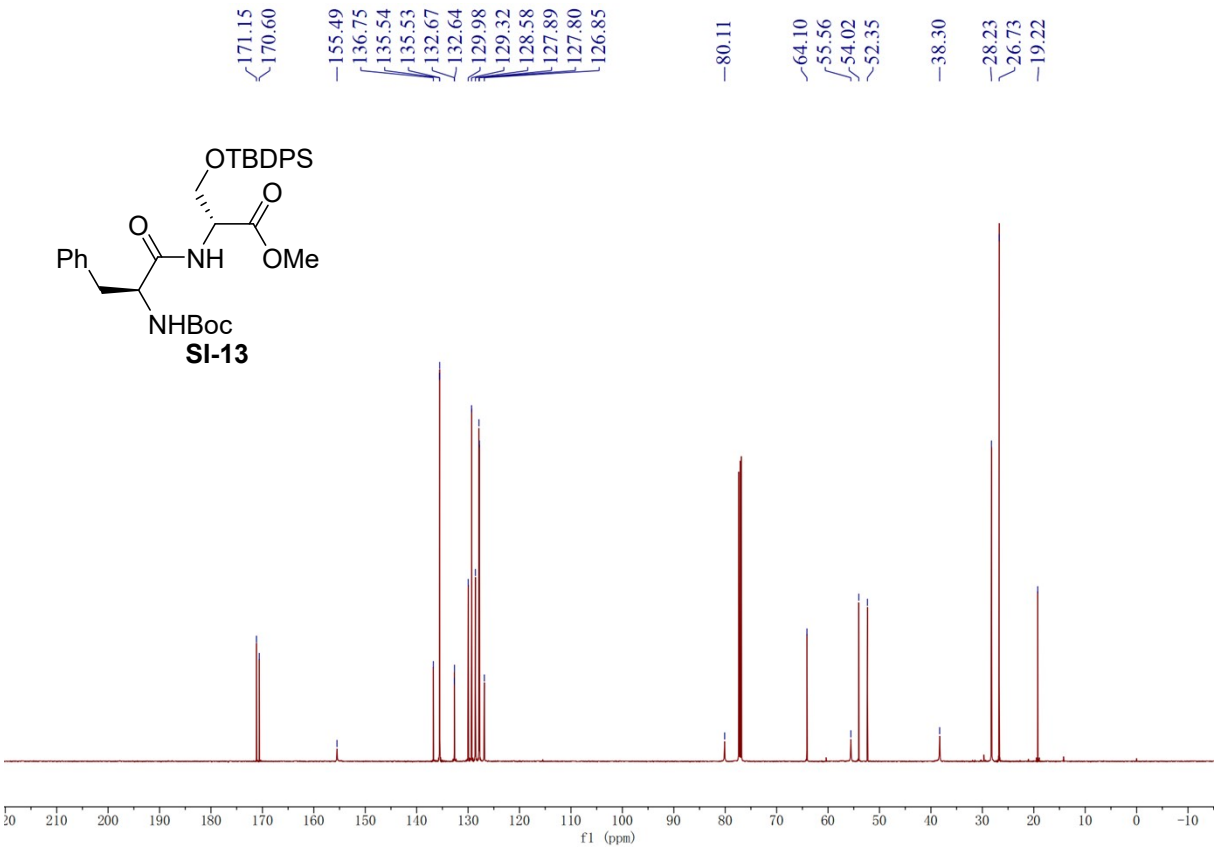
^{13}C NMR ($CDCl_3$, 126 MHz)



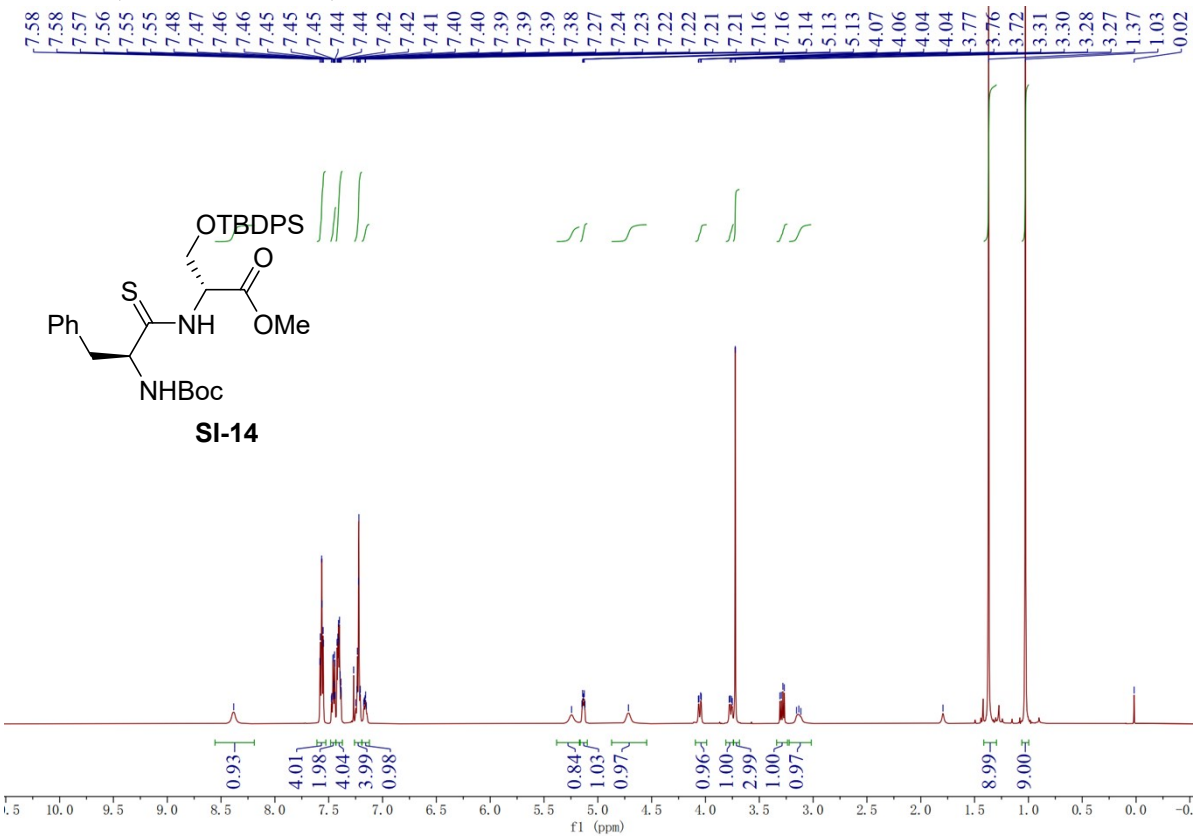
^{1}H NMR ($CDCl_3$, 500 MHz)



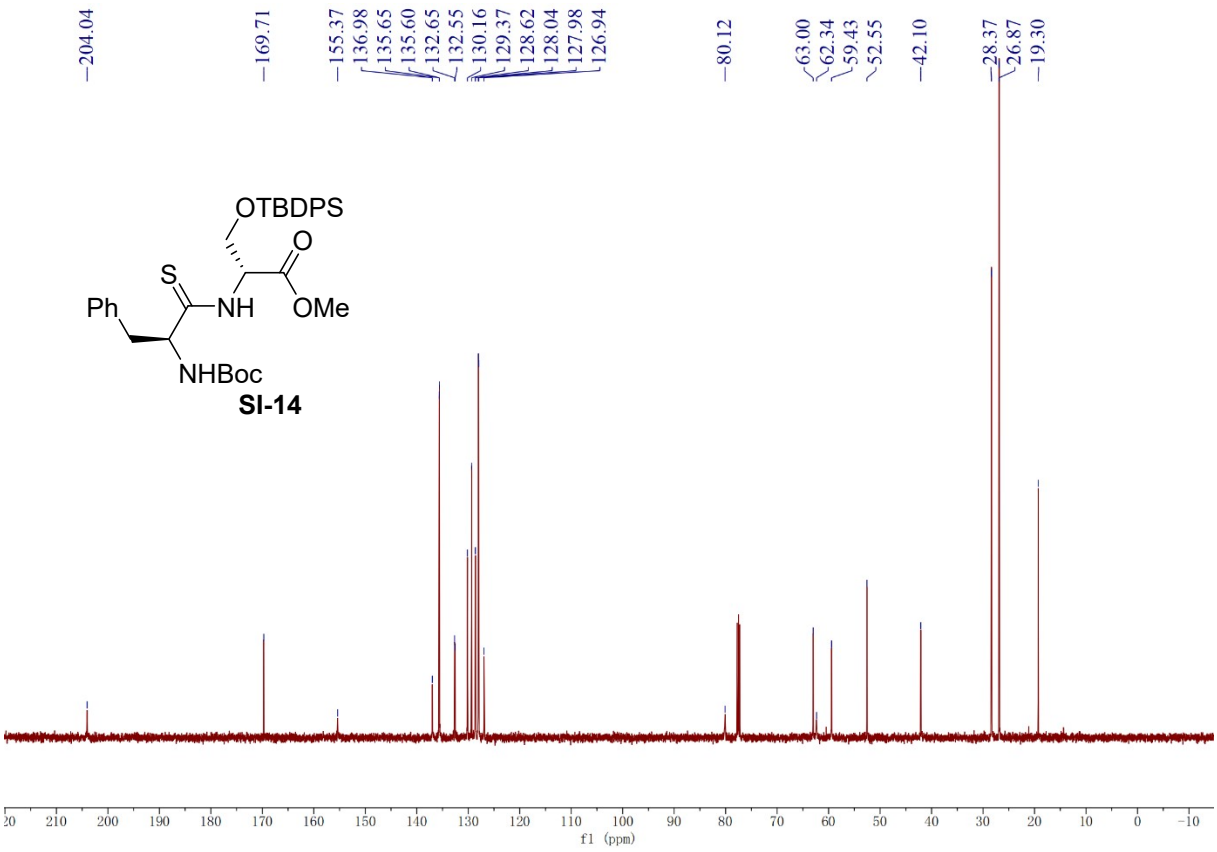
^{13}C NMR ($CDCl_3$, 126 MHz)



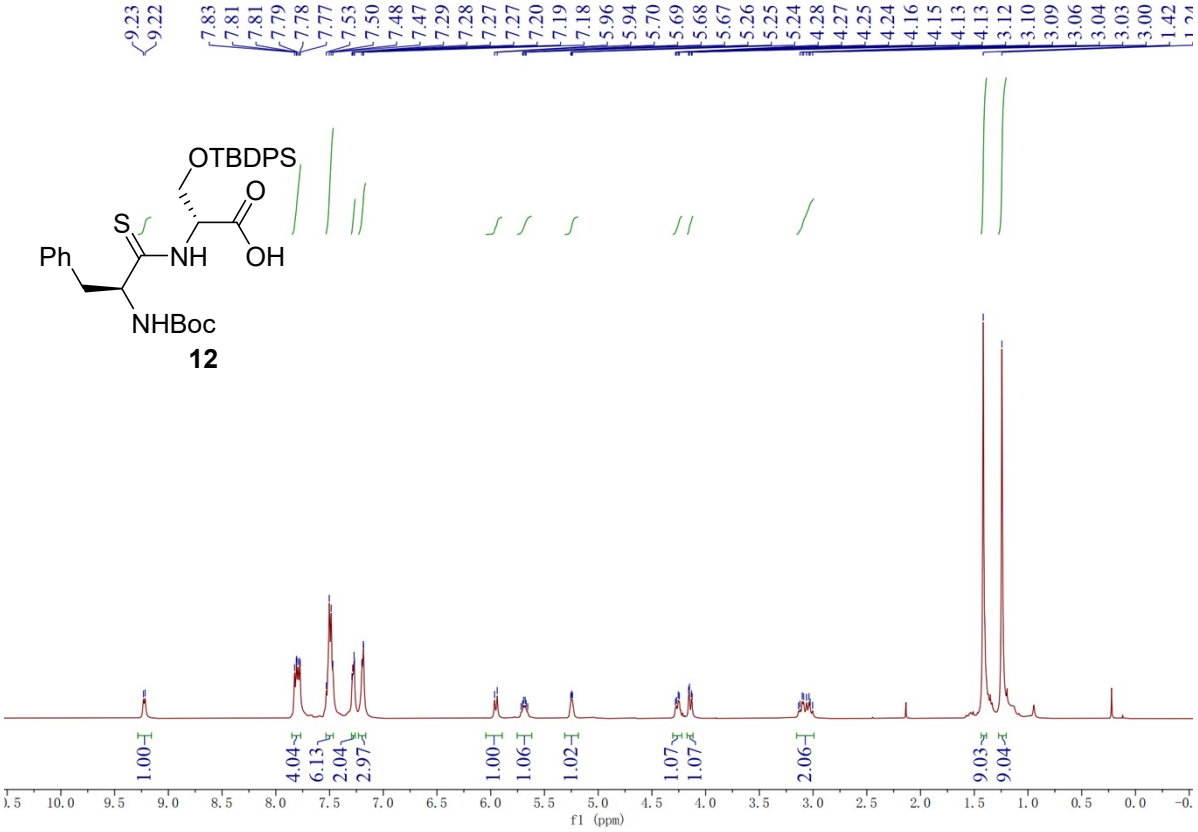
^{1}H NMR ($CDCl_3$, 500 MHz)



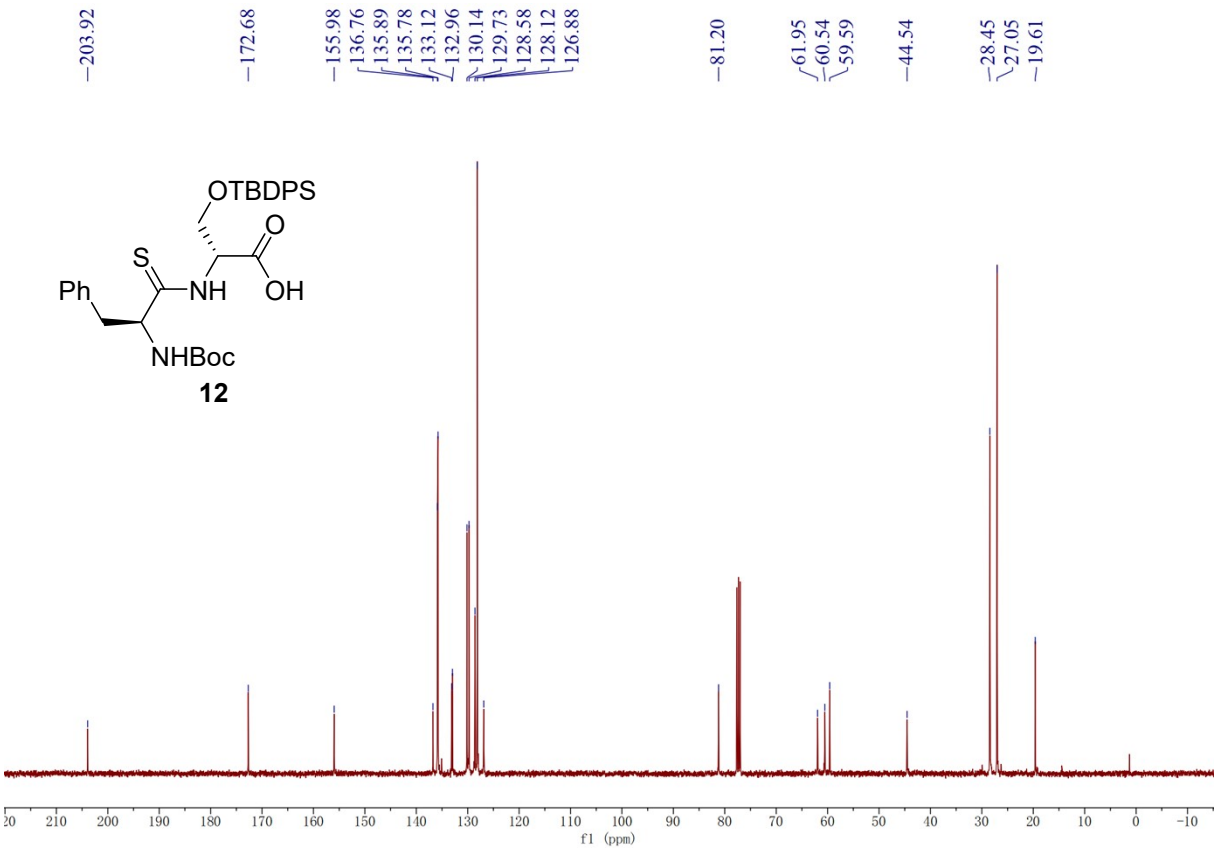
^{13}C NMR ($CDCl_3$, 126 MHz)



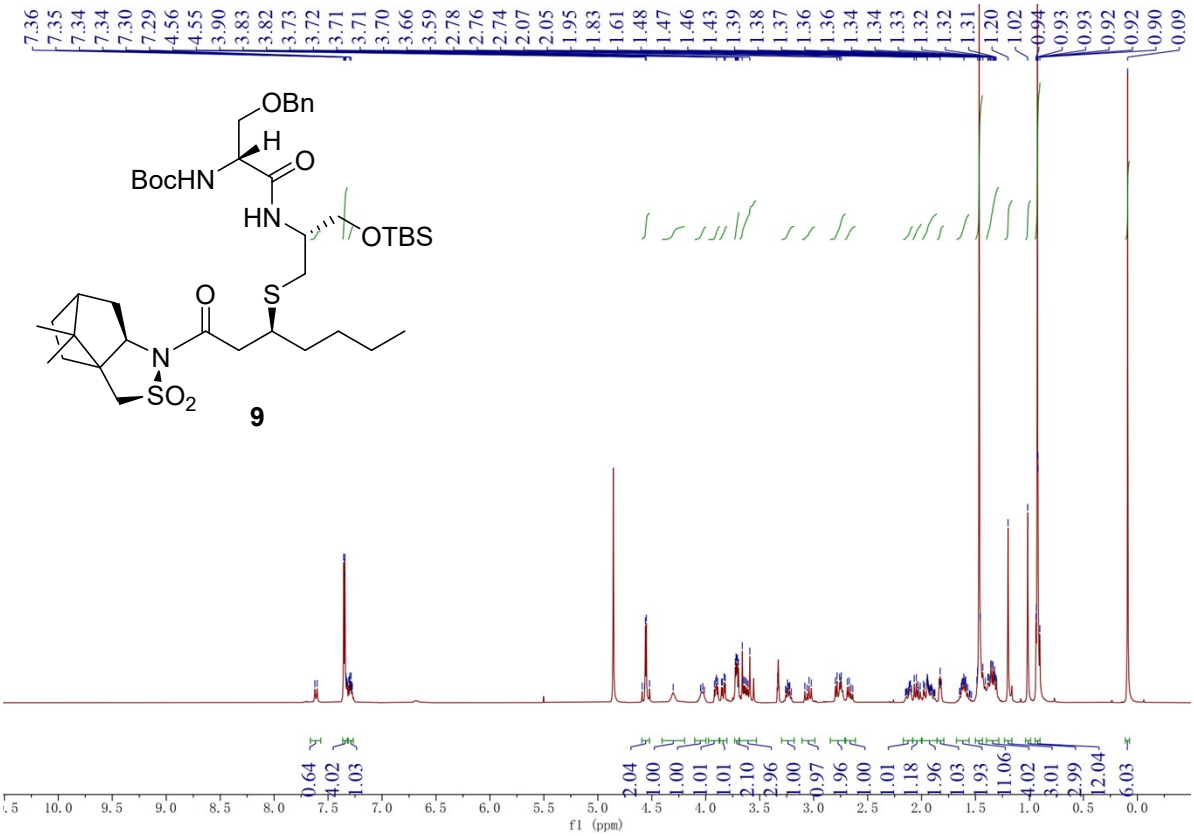
^{1}H NMR ($CDCl_3$, 400 MHz)



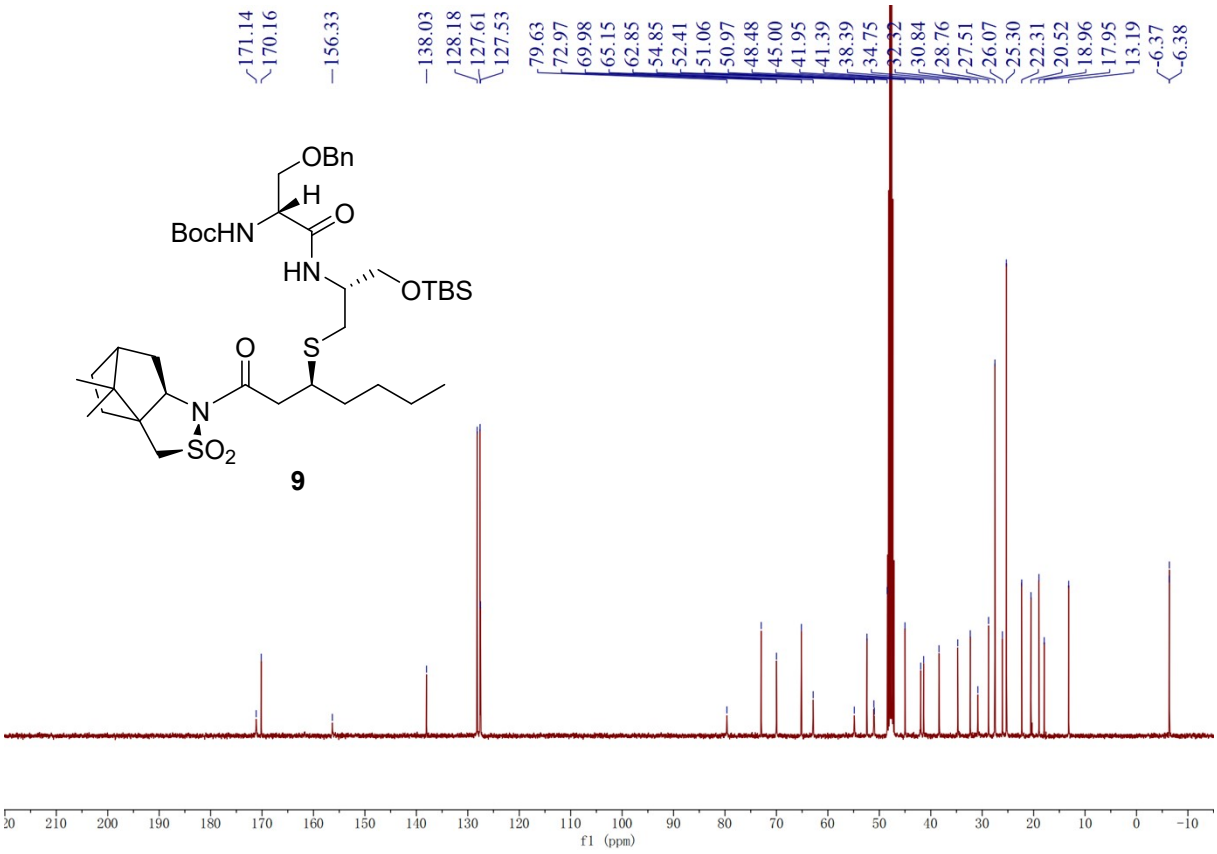
^{13}C NMR ($CDCl_3$, 101 MHz)



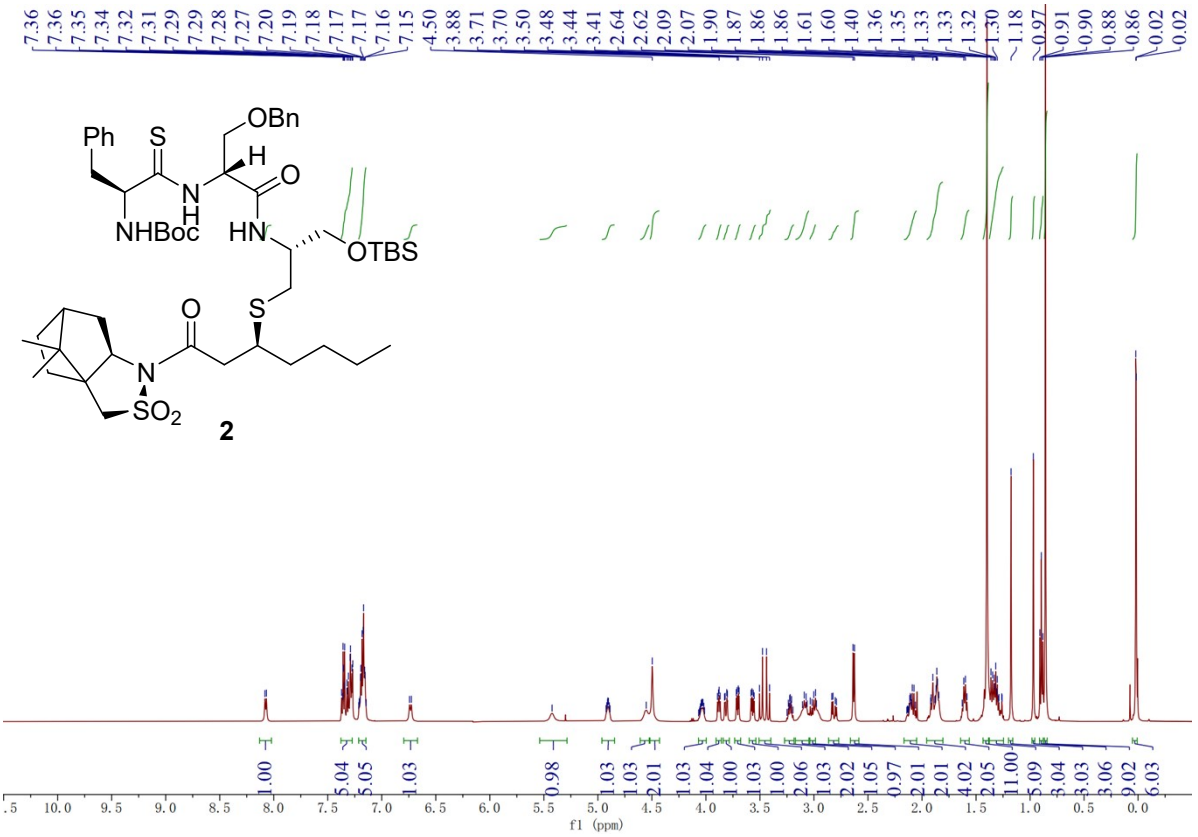
^{1}H NMR (CD_3OD, 400 MHz)



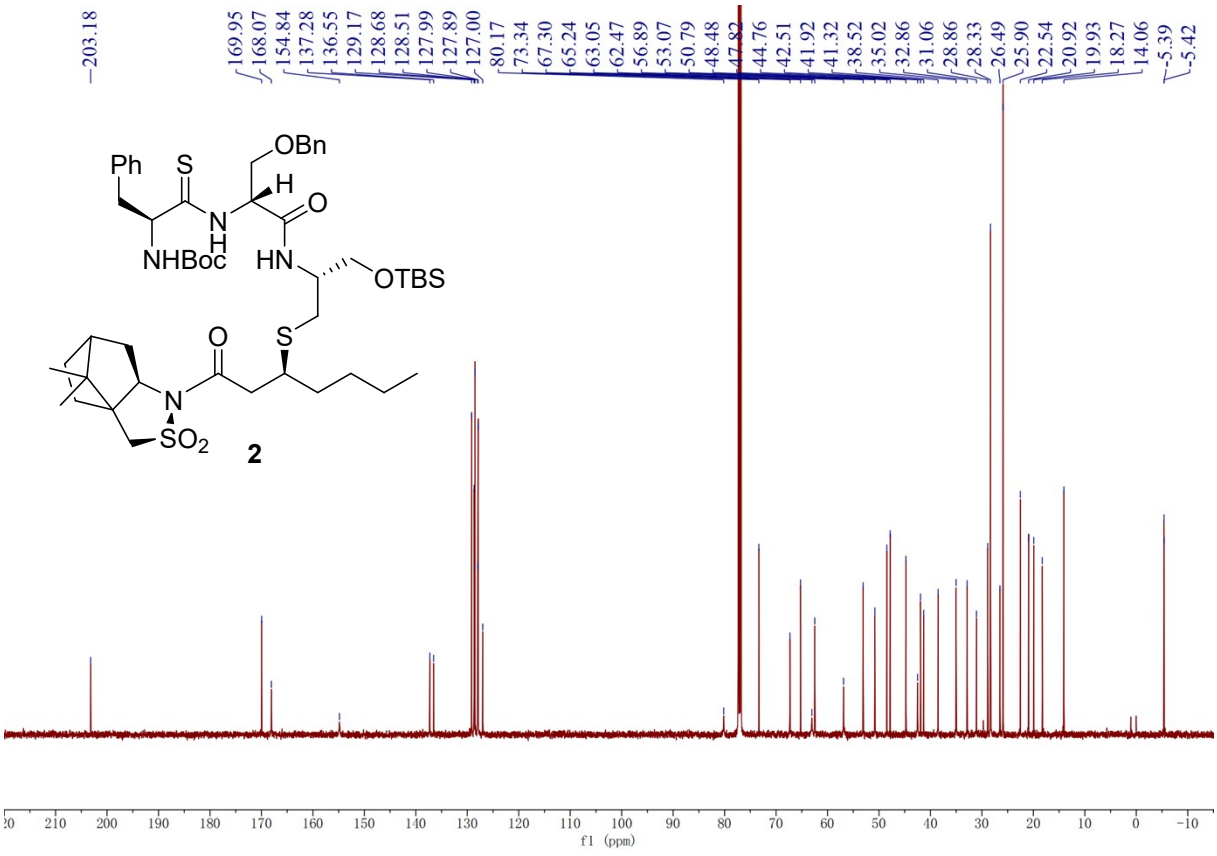
^{13}C NMR (CD_3OD, 101 MHz)



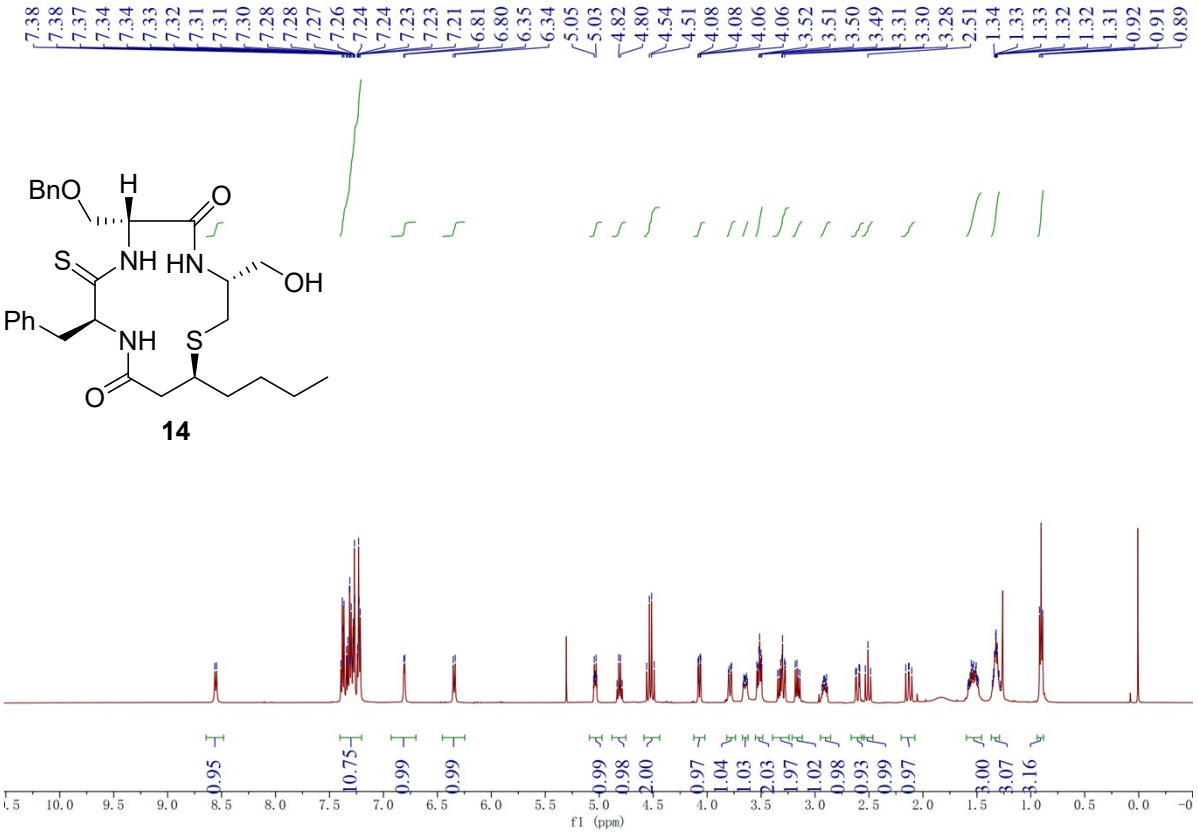
^{1}H NMR ($CDCl_3$, 500 MHz)



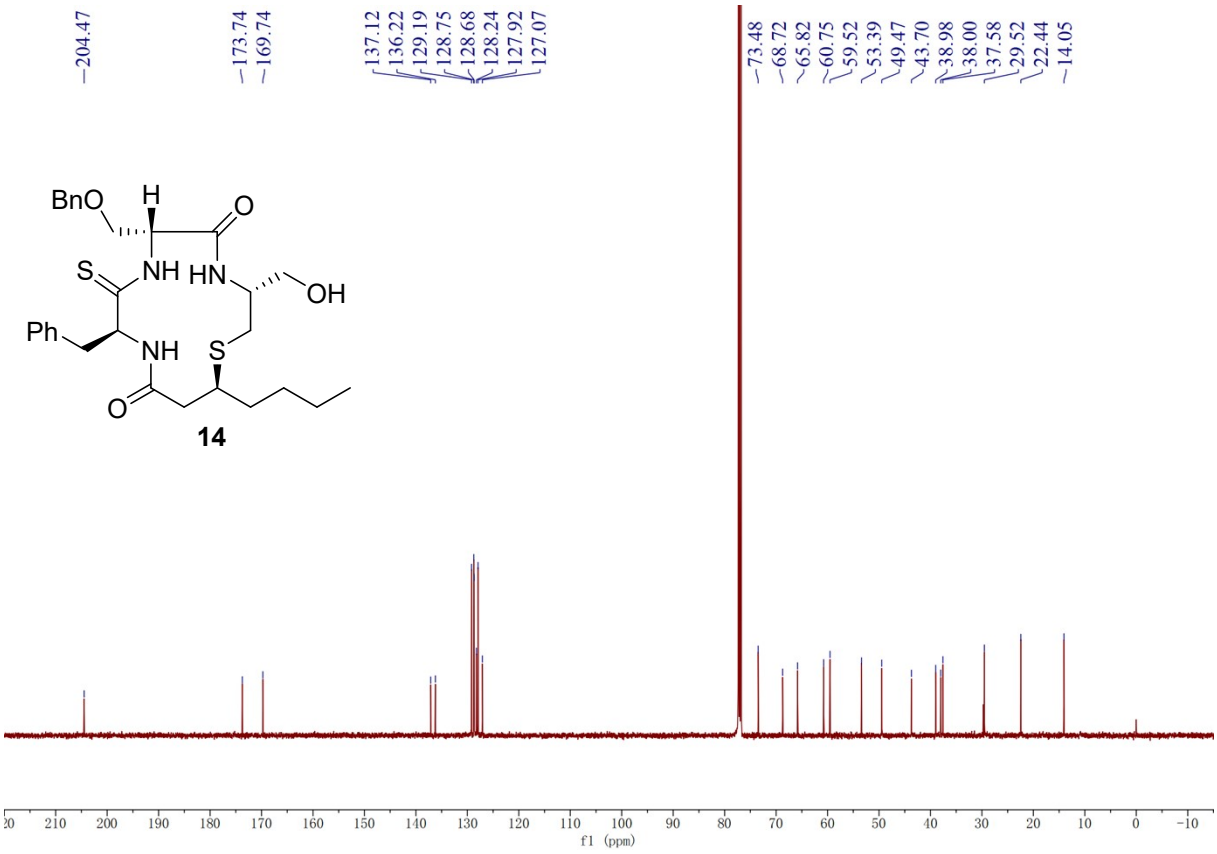
^{13}C NMR ($CDCl_3$, 126 MHz)



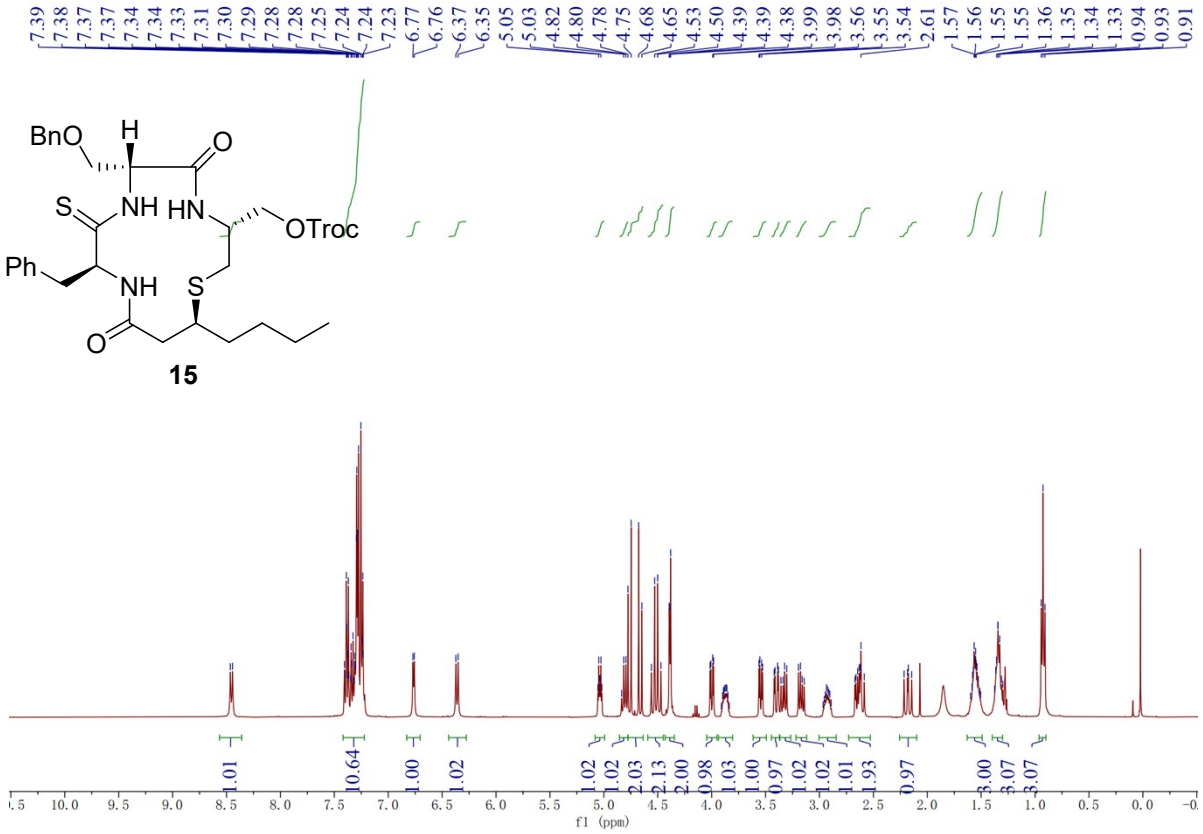
^{1}H NMR ($CDCl_3$, 500 MHz)



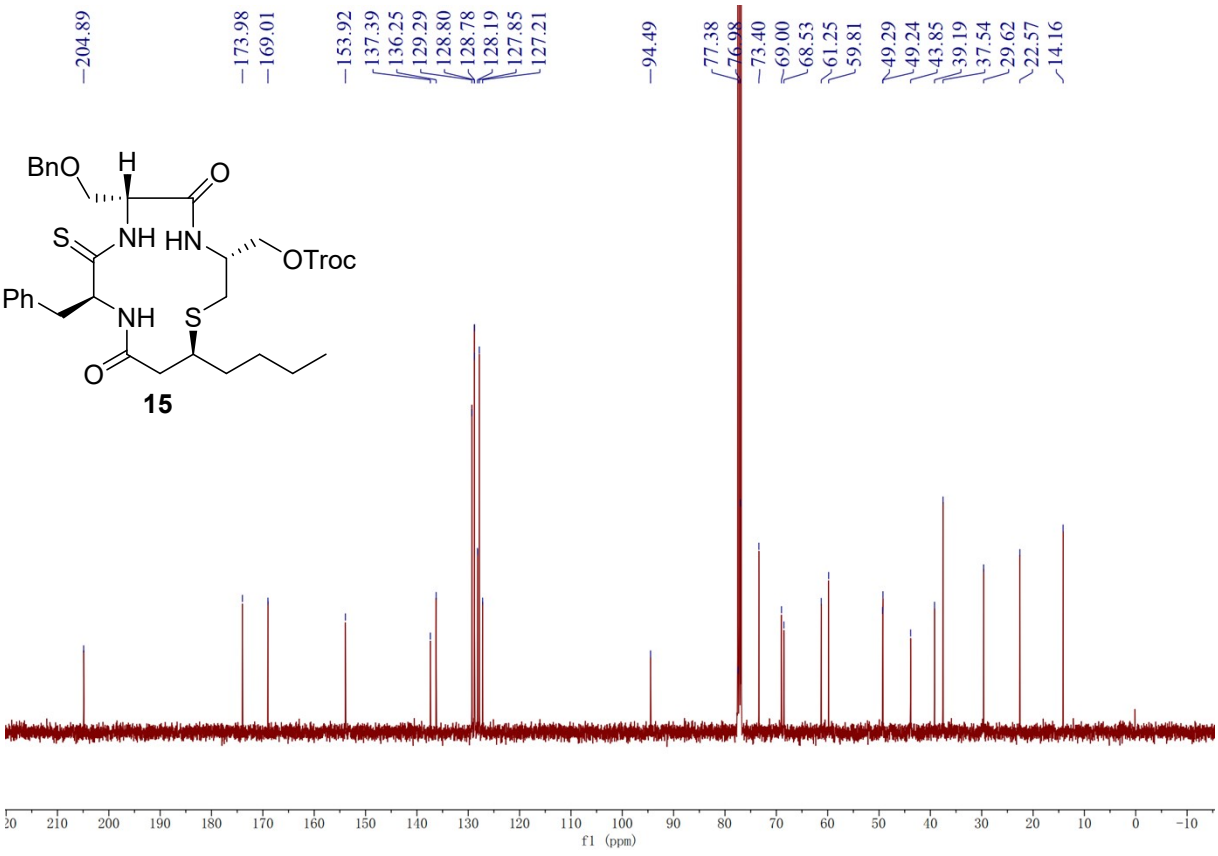
^{13}C NMR ($CDCl_3$, 126 MHz)



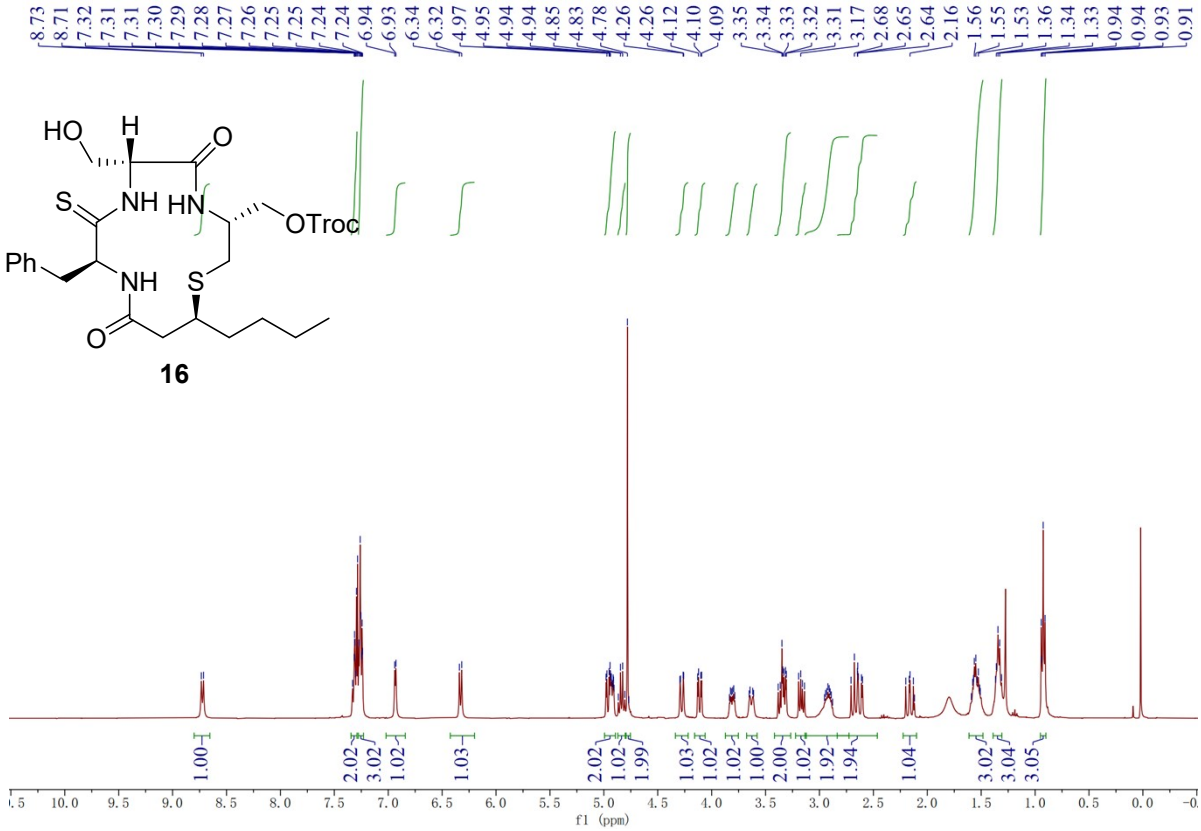
^{1}H NMR ($CDCl_3$, 400 MHz)



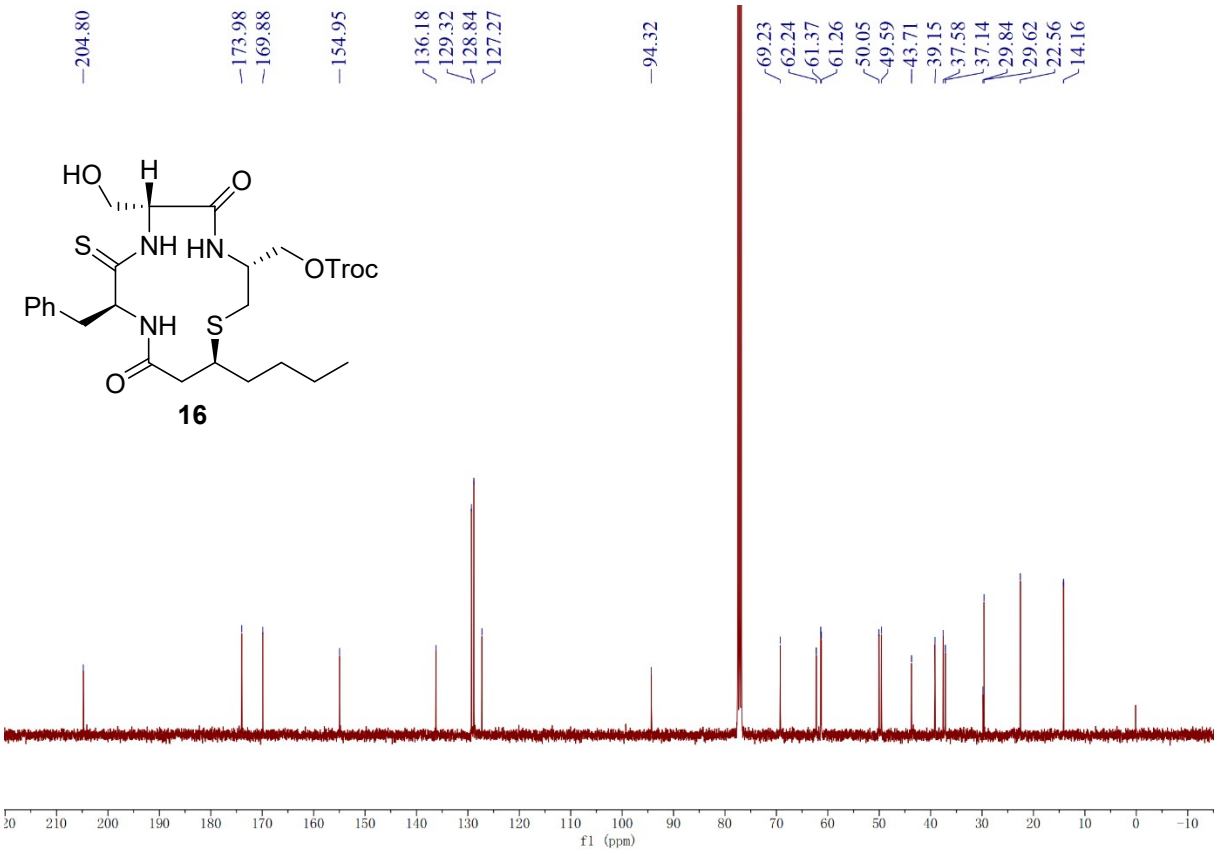
^{13}C NMR ($CDCl_3$, 101 MHz)



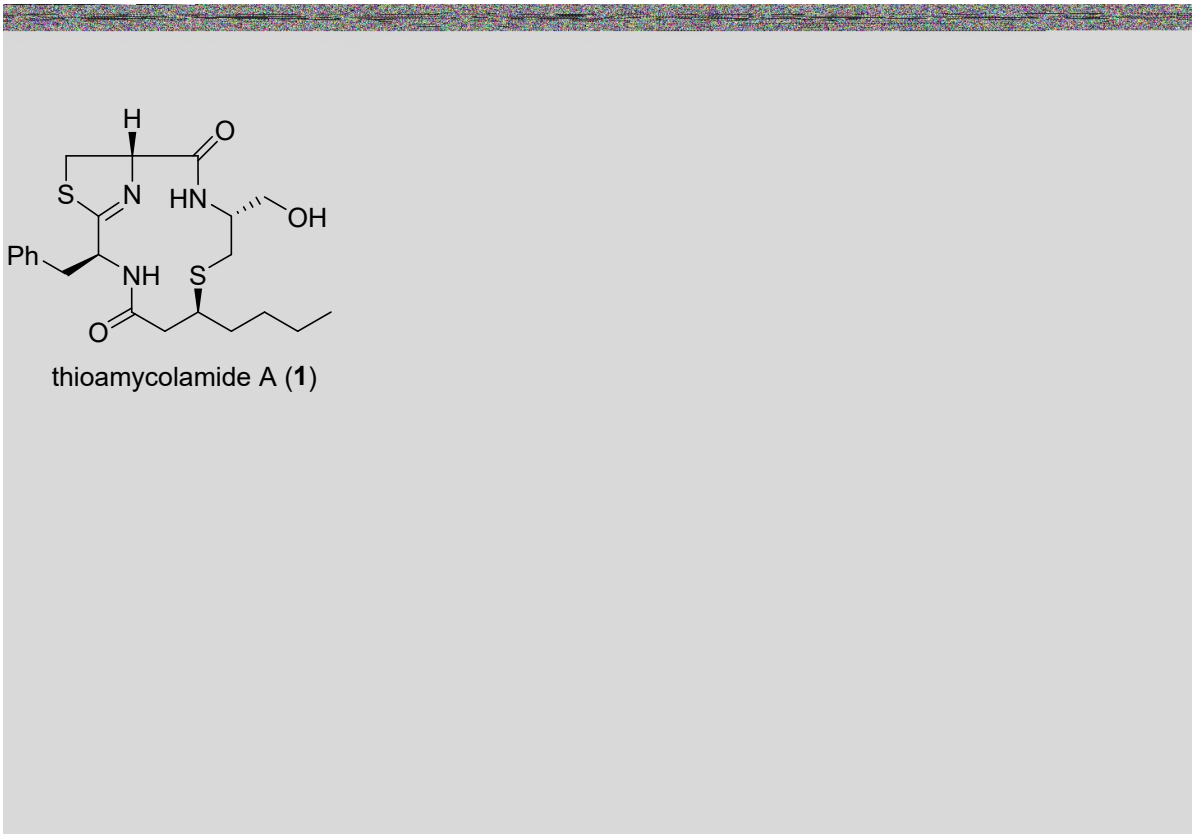
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 101 MHz)

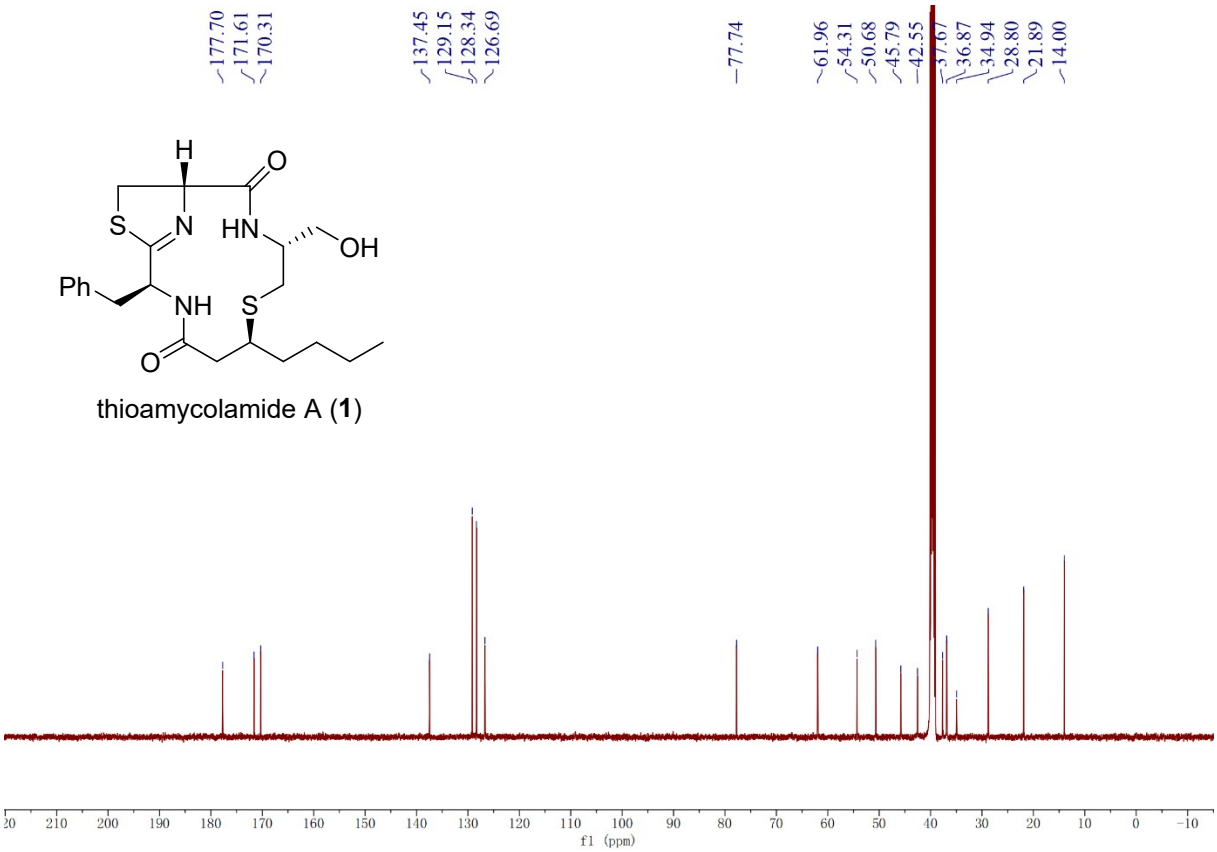


^{1}H NMR (DMSO-d_6, 500 MHz)



thioamycolamide A (**1**)

^{13}C NMR (DMSO-d_6, 126 MHz)



thioamycolamide A (**1**)

VI.Computational Methods

The sulfa-Michael addition reaction for the synthesis of the β-alkylthio carbonyl subunit in thioamycolamides was investigated using density functional theory (DFT). According to the experimental finding, the reaction became more selective when the Lewis acid (LiBr) was added. Therefore, the reactions were investigated in both with and without Li^+ ion to explain the selectivity of reaction and the role of Li^+ in the reaction process. The transition states of each *si*- and *re*-face attack were initially screened using ONIOM(QM1:QM2) technique which is calculated by ONIOM scheme in Gaussian 16 software.[1, 2] The Li^+ was used as a representation of Lewis acid in the reaction. In the presence of Li^+, of these initial 12 geometries (6 for each facial attack), only one geometry did not converged to transition state in the ONIOM(B3LYP/6-31+G(d,p):PM3). The remaining 11 geometries (6 for *si*-face and 5 for *re*-face attack) were used as an initial geometry for transition state search using B3LYP/6-31+G(d,p) level of theory.[3-6] Frequency calculations were done at the same level for each optimized structure to confirm the transition state (one imaginary frequency) and to obtain the thermodynamic correction. Obtained transition states were subjected to intrinsic reaction coordinate (IRC) calculations to connect each local minima. The subsequent endpoints of each forward and reverse direction were fully optimized together with frequency calculations at the same level to obtain the minima (no imaginary frequency). Only 9 geometries (5 for *si*-face and 4 for *re*-face attack) were successfully optimized. The same screening method was applied to the reaction without Li^+. The preliminary screening found that the structure is more flexible in the reaction without Li^+ than the one with Li^+. These 22 transition state (TS) structures, 11 structures for each facial attack, were obtained from the final QM calculations. All optimized stationary points were calculated using the M06-2x functional with 6-311+G(d,p) with Polarized Continuum Model (PCM) as solvation model (dichloromethane).[7-9]

From the theoretical point of view, the selectivity is related to the difference of Gibbs free energies of the transition state in each product formation.[10] The probability of existence for the transition states of each product formation is written as:

$$P(A_i) = \sum_i exp^{-\Delta\Delta G^{\ddagger}/RT}$$

$$\%selectivity = \frac{\sum_i P(A_i) - \sum_i P(B_i)}{\sum_i P(A_i) + \sum_i P(B_i)} \times 100$$

where $P(A_i)$ and $P(B_i)$ are percentages of existence for the i^{th} transition state of each product formation and $\Delta\Delta G^{\ddagger}$ is the Gibbs free energy relative to the most stable transition state, R is the gas constant, and T is the temperature in K (298.15 K).

Results and discussions:

It was found that the carbonyl oxygen of Boc group plays a crucial role in the reaction mechanism by coordinating with Li ion (Figure S1 and S2). The hydrogen bond between NH of substrate B and either Oppolzer O atom reduce the stability of the transition state. The relative free energies of each transition states are in range of 6 kcal/mol. The lowest energy of transition state of each *si*- and *re*-face attack is 1.70 kcal/mol apart in energy. We have calculated the probability of existence of each transition state as shown in Table S3. It was found that the most abundant transition state is *si*-face conf.1 at 94.81% followed by *re*-face conf.1

at 4.17% (Table S3). The calculated d.r. was found as 20.41:1, which is close to the experimental finding at 19:1. Assuming that each pathway is irrelevant (relative reactant complex energies for each pathway are 0.00 kcal/mol), three out of five *si*-face product formations have lower activation energy than *re*-face product formations (Figure S4). The experimental condition was under low temperature, which indicated that the reaction overcomes the lower activation barrier rather than higher one. These results are consistent with the experiment where the major product was the *si*-face attack.

In the reaction without Lewis acids, the experimental results showed that the d.r. was 1.4:1 at room temperature in dichloromethane solvent. The reaction with Lewis acids had a comparable yield but different d.r. Our calculations revealed the role and effect of Li^+ in stereoselectivity. Without Li^+, there is no center atom that hold both substrates together. Thus, substrate B could freely approach the olefin chain of Oppolzer which lower the difference between the lowest energy transition state of both reactions to 0.35 kcal/mol (Figure S9). Furthermore, there are six TS structures that contributed within 1 kcal/mol relative to the lowest transition state structure. The calculated d.r. is 1.81:1, which is in excellent agreement with the experimental data (Table S4). Compared to the reaction with Li^+, the activation energy is slightly increased and this reflected the comparable product yield of both systems. Therefore, the Li^+ does not reduce the activation energy of reaction which are around 23-29 kcal/mol and 26-33 kcal/mol in reactions with and without Li^+, respectively (Table S1, Table S2, Figure S3, and Figure S7). It indicates that Li^+ does not significantly reduce the activation energy for the sulfa-Michael addition, but acts as a center atom to induce the selectivity of the reaction by increasing the energy gap between the lowest transition state energy of both facial attacks.

Table S1. Raw energy data of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+

	B3LYP/6-31+G(d,p)					M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p)			
Reactant complex (RC)	E (a.u.)	ZPE (a.u.)	Δ(E+ZPE) (kcal/mol)	G-correction (a.u.)	ΔG (kcal/mol)	ΔE (kcal/mol)	E (a.u.)	Δ(E+ZPE) (kcal/mol)	ΔG (kcal/mol)
si-face conf.1	-2870.592931	0.865987	-0.02	0.770297	0.00	0.13	-2870.203725	0.12	0.06
si-face conf.2	-2870.580938	0.866087	7.57	0.769516	7.04	2.56	-2870.199844	2.62	2.00
si-face conf.3	-2870.575905	0.866199	10.80	0.770590	10.87	4.24	-2870.197179	4.36	4.35
si-face conf.4	-2870.585061	0.866229	5.08	0.771025	5.40	2.89	-2870.199323	3.03	3.28
si-face conf.5	-2870.562146	0.865447	18.96	0.765103	16.06	12.70	-2870.183687	12.35	9.37
re-face conf.1	-2870.592922	0.866003	0.00	0.770410	0.08	0.00	-2870.203928	0.00	0.00
re-face conf.2	-2870.580761	0.866100	7.69	0.770932	8.04	2.50	-2870.199937	2.57	2.83
re-face conf.3	-2870.583391	0.865697	5.79	0.766551	3.64	5.74	-2870.194774	5.55	3.32
re-face conf.4	-2870.591890	0.866054	0.68	0.770475	0.76	0.57	-2870.203022	0.60	0.61
Transition state (TS)									
si-face conf.1	-2870.548024	0.865946	28.14	0.777195	32.51	18.79	-2870.173984	18.75	23.05
si-face conf.2	-2870.532457	0.866228	38.08	0.776873	42.07	25.15	-2870.163846	25.29	29.21
si-face conf.3	-2870.537622	0.866334	34.91	0.778698	39.98	20.67	-2870.170987	20.88	25.87
si-face conf.4	-2870.534372	0.865226	36.25	0.776353	40.55	24.78	-2870.164435	24.29	28.51
si-face conf.5	-2870.508724	0.864645	51.98	0.771800	53.78	27.85	-2870.159546	27.00	28.72
re-face conf.1	-2870.545630	0.865463	29.34	0.775753	33.11	21.39	-2870.169839	21.05	24.74
re-face conf.2	-2870.535374	0.866179	36.22	0.777549	40.67	23.38	-2870.166670	23.49	27.86
re-face conf.3	-2870.539522	0.865317	33.08	0.776379	37.33	22.95	-2870.167355	22.52	26.70
re-face conf.4	-2870.542787	0.865614	31.22	0.776493	35.35	22.25	-2870.168468	22.01	26.07

Table S1. Raw energy data of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+ (cont.)

	B3LYP/6-31+G(d,p)					M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p)			
Intermediate (Int)	E (a.u.)	ZPE (a.u.)	Δ(E+ZPE) (kcal/mol)	G-correction (a.u.)	ΔG (kcal/mol)	ΔE (kcal/mol)	E (a.u.)	Δ(E+ZPE) (kcal/mol)	ΔG (kcal/mol)
si-face conf.1	-2870.566983	0.870321	18.99	0.780591	22.74	1.25	-2870.201935	3.96	7.64
si-face conf.2	-2870.555564	0.870817	26.46	0.782405	31.05	3.74	-2870.197967	6.76	11.27
si-face conf.3	-2870.555165	0.870821	26.72	0.782426	31.31	3.94	-2870.197643	6.97	11.48
si-face conf.4	-2870.548950	0.869825	29.99	0.780606	34.07	10.28	-2870.187549	12.68	16.68
si-face conf.5	-2870.518121	0.868549	48.54	0.774467	49.56	14.51	-2870.180804	16.11	17.06
re-face conf.1	-2870.562389	0.869808	21.55	0.779397	24.88	5.10	-2870.195804	7.49	10.74
re-face conf.2	-2870.556191	0.870933	26.14	0.782928	30.98	2.84	-2870.199397	5.94	10.70
re-face conf.3	-2870.554607	0.869902	26.49	0.780865	30.68	7.14	-2870.192551	9.59	13.70
re-face conf.4	-2870.561077	0.869950	22.46	0.779828	25.97	4.70	-2870.196438	7.18	10.61

Table S2. Raw energy data of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+

	B3LYP/6-31+G(d,p)					M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p)			
Reactant complex (RC)	E (a.u.)	ZPE (a.u.)	Δ(E+ZPE) (kcal/mol)	G-correction (a.u.)	ΔG (kcal/mol)	ΔE (kcal/mol)	E (a.u.) (kcal/mol)	Δ(E+ZPE) (kcal/mol)	ΔG (kcal/mol)
si-face conf.1	-2863.123537	0.862290	7.17	0.764960	5.88	4.88	-2862.713066	4.79	4.65
si-face conf.2	-2863.124086	0.862736	7.10	0.768839	7.97	4.06	-2862.714376	4.25	6.26
si-face conf.3	-2863.118187	0.861921	10.29	0.764413	8.89	8.89	-2862.706666	8.58	8.32
si-face conf.4	-2863.135402	0.862797	0.04	0.767874	0.26	0.05	-2862.720756	0.28	1.65
si-face conf.5	-2863.125856	0.862012	5.54	0.765866	4.99	4.06	-2862.714364	3.80	4.40
si-face conf.6	-2863.122696	0.862298	7.70	0.765179	6.54	4.76	-2862.713256	4.68	4.66
si-face conf.7	-2863.135385	0.862719	0.00	0.767444	0.00	0.00	-2862.720841	0.18	1.33
si-face conf.8	-2863.124089	0.862204	6.77	0.767355	7.03	3.10	-2862.715896	2.96	4.37
si-face conf.9	-2863.128155	0.861931	4.04	0.765239	3.15	2.58	-2862.716721	2.27	2.53
si-face conf.10	-2863.128952	0.862109	3.65	0.766094	3.19	1.12	-2862.719057	0.92	1.60
si-face conf.11	-2863.126280	0.862326	5.47	0.765115	4.25	4.29	-2862.713999	4.23	4.16
re-face conf.1	-2863.125448	0.862371	6.02	0.765512	5.02	4.04	-2862.714409	4.00	4.15
re-face conf.2	-2863.131892	0.862492	2.05	0.767122	1.99	1.93	-2862.717771	1.97	3.05
re-face conf.3	-2863.130744	0.862183	2.58	0.766203	2.13	0.60	-2862.719878	0.45	1.15
re-face conf.4	-2863.130887	0.862288	2.55	0.766923	2.50	0.57	-2862.719940	0.48	1.56
re-face conf.5	-2863.124178	0.862023	6.60	0.765372	5.73	5.73	-2862.711715	5.47	5.75
re-face conf.6	-2863.122689	0.862242	7.67	0.765043	6.46	5.07	-2862.712766	4.95	4.89
re-face conf.7	-2863.126388	0.862264	5.36	0.765080	4.16	4.19	-2862.714157	4.09	4.04
re-face conf.8	-2863.131217	0.861971	2.15	0.763693	0.26	1.03	-2862.719202	0.74	0.00
re-face conf.9	-2863.130857	0.862195	2.51	0.766048	1.97	0.69	-2862.719738	0.54	1.14
re-face conf.10	-2863.132232	0.862247	1.68	0.765320	0.65	0.11	-2862.720658	0.00	0.11
re-face conf.11	-2863.128203	0.862084	4.11	0.765318	3.17	3.46	-2862.715329	3.24	3.45

Table S2. Raw energy data of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+ (cont.)

	B3LYP/6-31+G(d,p)					M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p)			
Transition state (TS)	E (a.u.)	ZPE (a.u.)	Δ(E+ZPE) (kcal/mol)	G-correction (a.u.)	ΔG (kcal/mol)	ΔE (kcal/mol)	E (a.u.) (kcal/mol)	Δ(E+ZPE) (kcal/mol)	ΔG (kcal/mol)
si-face conf.1	-2863.086222	0.860473	29.44	0.768686	31.63	25.73	-2862.67983	24.51	27.84
si-face conf.2	-2863.080864	0.860268	32.67	0.769985	35.81	27.50	-2862.677012	26.15	30.42
si-face conf.3	-2863.080717	0.859641	32.37	0.767121	34.10	30.49	-2862.672249	28.74	31.61
si-face conf.4	-2863.094111	0.863107	26.14	0.773666	29.80	23.39	-2862.683573	23.81	28.62
si-face conf.5	-2863.090197	0.860291	26.83	0.767711	28.52	25.36	-2862.680423	24.02	26.86
si-face conf.6	-2863.084695	0.860296	30.29	0.768502	32.47	27.82	-2862.676506	26.48	29.81
si-face conf.7	-2863.089574	0.861005	27.67	0.767852	29.00	26.34	-2862.678866	25.45	27.92
si-face conf.8	-2863.086384	0.860466	29.33	0.771252	33.14	25.14	-2862.680780	23.91	28.85
si-face conf.9	-2863.089058	0.859935	27.32	0.767198	28.92	26.77	-2862.678185	25.20	27.94
si-face conf.10	-2863.090954	0.860479	26.48	0.770595	29.86	23.35	-2862.683637	22.12	26.65
si-face conf.11	-2863.089902	0.860486	27.14	0.768842	29.42	25.88	-2862.679602	24.66	28.08
re-face conf.1	-2863.082651	0.860470	31.68	0.768115	33.51	29.90	-2862.673197	28.67	31.64
re-face conf.2	-2863.085045	0.860171	29.99	0.768060	31.98	27.95	-2862.676306	26.53	29.66
re-face conf.3	-2863.085698	0.859920	29.42	0.765639	30.05	28.42	-2862.675546	26.85	28.62
re-face conf.4	-2863.086172	0.861063	29.84	0.768149	31.32	28.55	-2862.675345	27.69	30.32
re-face conf.5	-2863.086335	0.859840	28.97	0.768506	31.45	27.28	-2862.677370	25.65	29.27
re-face conf.6	-2863.078600	0.859819	33.81	0.766952	35.32	32.13	-2862.669641	30.49	33.14
re-face conf.7	-2863.084874	0.859663	29.78	0.765925	30.74	29.08	-2862.674501	27.34	29.45
re-face conf.8	-2863.090155	0.860043	26.70	0.767260	28.27	25.79	-2862.679737	24.30	27.00
re-face conf.9	-2863.086362	0.860520	29.38	0.767083	30.54	28.67	-2862.675153	27.47	29.77
re-face conf.10	-2863.088423	0.859799	27.64	0.766904	29.13	26.59	-2862.678463	24.94	27.58
re-face conf.11	-2863.089732	0.860168	27.05	0.767861	28.91	25.54	-2862.680134	24.12	27.13

Table S2. Raw energy data of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+ (cont.)

Intermediate (Int)	B3LYP/6-31+G(d,p)					M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p)			
	E (a.u.)	ZPE (a.u.)	Δ(E+ZPE) (kcal/mol)	G-correction (a.u.)	ΔG (kcal/mol)	ΔE (kcal/mol)	E (a.u.) (kcal/mol)	Δ(E+ZPE) (kcal/mol)	ΔG (kcal/mol)
si-face conf.1	-2863.115345	0.867053	15.30	0.776547	18.29	2.01	-2862.717634	4.91	9.05
si-face conf.2	-2863.108240	0.866931	19.68	0.776641	22.81	4.83	-2862.713142	7.66	11.93
si-face conf.3	-2863.108129	0.866517	19.49	0.775273	22.02	7.01	-2862.709677	9.57	13.24
si-face conf.4	-2863.116672	0.867331	14.64	0.776961	17.71	1.90	-2862.717814	4.97	9.20
si-face conf.5	-2863.117202	0.866775	13.96	0.774230	15.67	2.89	-2862.716241	5.61	8.47
si-face conf.6	-2863.113489	0.866924	16.38	0.777483	20.04	2.56	-2862.716764	5.38	10.18
si-face conf.7	-2863.116651	0.867179	14.55	0.775769	16.98	1.95	-2862.717730	4.93	8.50
si-face conf.8	-2863.112332	0.866924	17.10	0.778939	21.68	2.52	-2862.716824	5.34	11.06
si-face conf.9	-2863.116884	0.866474	13.97	0.774557	16.07	1.51	-2862.718432	4.05	7.30
si-face conf.10	-2863.117255	0.866711	13.88	0.777514	17.70	0.64	-2862.719818	3.33	8.29
si-face conf.11	-2863.115884	0.866960	14.90	0.776059	17.64	3.37	-2862.715477	6.21	10.10
re-face conf.1	-2863.107609	0.866502	19.80	0.773800	21.42	7.64	-2862.708667	10.19	12.95
re-face conf.2	-2863.108450	0.866389	19.20	0.774557	21.37	7.03	-2862.709641	9.51	12.82
re-face conf.3	-2863.111600	0.866102	17.05	0.772320	17.99	6.13	-2862.711074	8.43	10.51
re-face conf.4	-2863.112923	0.865987	16.15	0.770733	16.16	5.61	-2862.711907	7.84	9.00
re-face conf.5	-2863.113365	0.866319	16.08	0.775500	18.87	3.51	-2862.715243	5.95	9.89
re-face conf.6	-2863.104194	0.866287	21.81	0.773632	23.46	9.23	-2862.706125	11.65	14.44
re-face conf.7	-2863.111145	0.866118	17.34	0.773552	19.04	5.49	-2862.712087	7.81	10.65
re-face conf.8	-2863.113772	0.866062	15.66	0.773215	17.18	4.15	-2862.714223	6.43	9.10
re-face conf.9	-2863.112940	0.866096	16.20	0.771859	16.85	5.63	-2862.711874	7.93	9.72
re-face conf.10	-2863.114925	0.866335	15.11	0.773372	16.56	4.61	-2862.713500	7.06	9.65
re-face conf.11	-2863.114653	0.866332	15.28	0.774838	17.65	4.80	-2862.713190	7.25	10.77

Table S3. Relative free energies ($\Delta G^{\ddagger}$, $\Delta\Delta G^{\ddagger}$) of *si*- and *re*-face transition state (TS) conformations and probability (*P*) of transition states of the sulfa-Michael addition reaction in thioamycolamide A synthesis with Li^{+}.

	$\Delta G^{\ddagger a}$ (kcal/mol)	$\Delta\Delta G^{\ddagger b}$ (kcal/mol)	Probabilities of TS conformers[c] (%)	Sum of probabilities (%)
si-face conf.1	23.05	0.00	94.81	95.34
si-face conf.2	29.21	6.16	0.00	
si-face conf.3	25.87	2.82	0.52	
si-face conf.4	28.51	5.46	0.00	
si-face conf.5	28.72	5.67	0.00	
re-face conf.1	24.74	1.70	4.17	4.66
re-face conf.2	27.86	4.81	0.01	
re-face conf.3	26.70	3.65	0.11	
re-face conf.4	26.07	3.02	0.36	
Calculated diastereomeric ratio (d.r.) of *si*-face:*re*-face TSs[d]				20.46 : 1
Experimental diastereomeric ratio (d.r.) of *si*-face:*re*-face TSs				19 : 1

Energies were calculated at M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level (kcal/mol) in dichloromethane.

[a] $\Delta G^{\ddagger}$ is the free energy relative to that of the lowest energy reactant complex (*re*-face conf.1).

[b] $\Delta\Delta G^{\ddagger}$ is the free energy relative to that of the lowest energy transition state (*si*-face conf.1).

[c] Probabilities of transition state conformers are calculated using $P(A_i) = exp^{-\Delta\Delta G^{\ddagger}/RT}$, where A_i is the i^{th} individual transition state.

[d] The diastereomeric ratio (d.r.) is calculated using $d.r. = \sum_i P\,(si-face\ conf.i) : \sum_i P\,(re-face\ conf.i)$

Table S4. Relative free energies ($\Delta G^{\ddagger}$, $\Delta\Delta G^{\ddagger}$) of *si*- and *re*-face transition state (TS) conformations and probability (*P*) of transition states of the sulfa-Michael addition reaction in thioamycolamide A synthesis with Li^{+}.

	$\Delta G^{\ddagger a}$ (kcal/mol)	$\Delta\Delta G^{\ddagger b}$ (kcal/mol)	Probabilities of TS conformers[c] (%)	Sum of probabilities (%)
si-face conf.1	27.84	1.19	3.42	
si-face conf.2	30.42	3.77	0.03	
si-face conf.3	31.61	4.97	0.00	
si-face conf.4	28.62	1.97	0.82	
si-face conf.5	26.86	0.21	20.92	
si-face conf.6	29.81	3.16	0.09	64.44
si-face conf.7	27.92	1.27	2.94	
si-face conf.8	28.85	2.21	0.53	
si-face conf.9	27.94	1.29	2.85	
si-face conf.10	26.65	0.00	30.65	
si-face conf.11	28.08	1.43	2.19	
re-face conf.1	31.64	4.99	0.00	
re-face conf.2	29.66	3.01	0.12	
re-face conf.3	28.62	1.97	0.82	
re-face conf.4	30.32	3.67	0.04	
re-face conf.5	29.27	2.62	0.24	
re-face conf.6	33.14	6.50	0.00	35.56
re-face conf.7	29.45	2.80	0.18	
re-face conf.8	27.00	0.35	15.95	
re-face conf.9	29.78	3.12	0.10	
re-face conf.10	27.58	0.93	5.52	
re-face conf.11	27.13	0.48	12.59	
Calculated diastereomeric ratio (d.r.) of *si*-face:*re*-face TSs[d]				1.81 : 1
Experimental diastereomeric ratio (d.r.) of *si*-face:*re*-face TSs				1.4 : 1

Energies were calculated at M06-2x(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level (kcal/mol) in dichloromethane.

[a] $\Delta G^{\ddagger}$ is the free energy relative to that of the lowest energy reactant complex (*re*-face conf.8).

[b] $\Delta\Delta G^{\ddagger}$ is the free energy relative to that of the lowest energy transition state (*si*-face conf.10).

[c] Probabilities of transition state conformers are calculated using $P(A_i) = exp^{-\Delta\Delta G^{\ddagger}/RT}$, where A_i is the i^{th} individual individual transition state.

[d] The diastereomeric ratio (d.r.) is calculated using $d.r. = \sum_i P\,(si-face\ conf.i) : \sum_i P\,(re-face\ conf.i)$

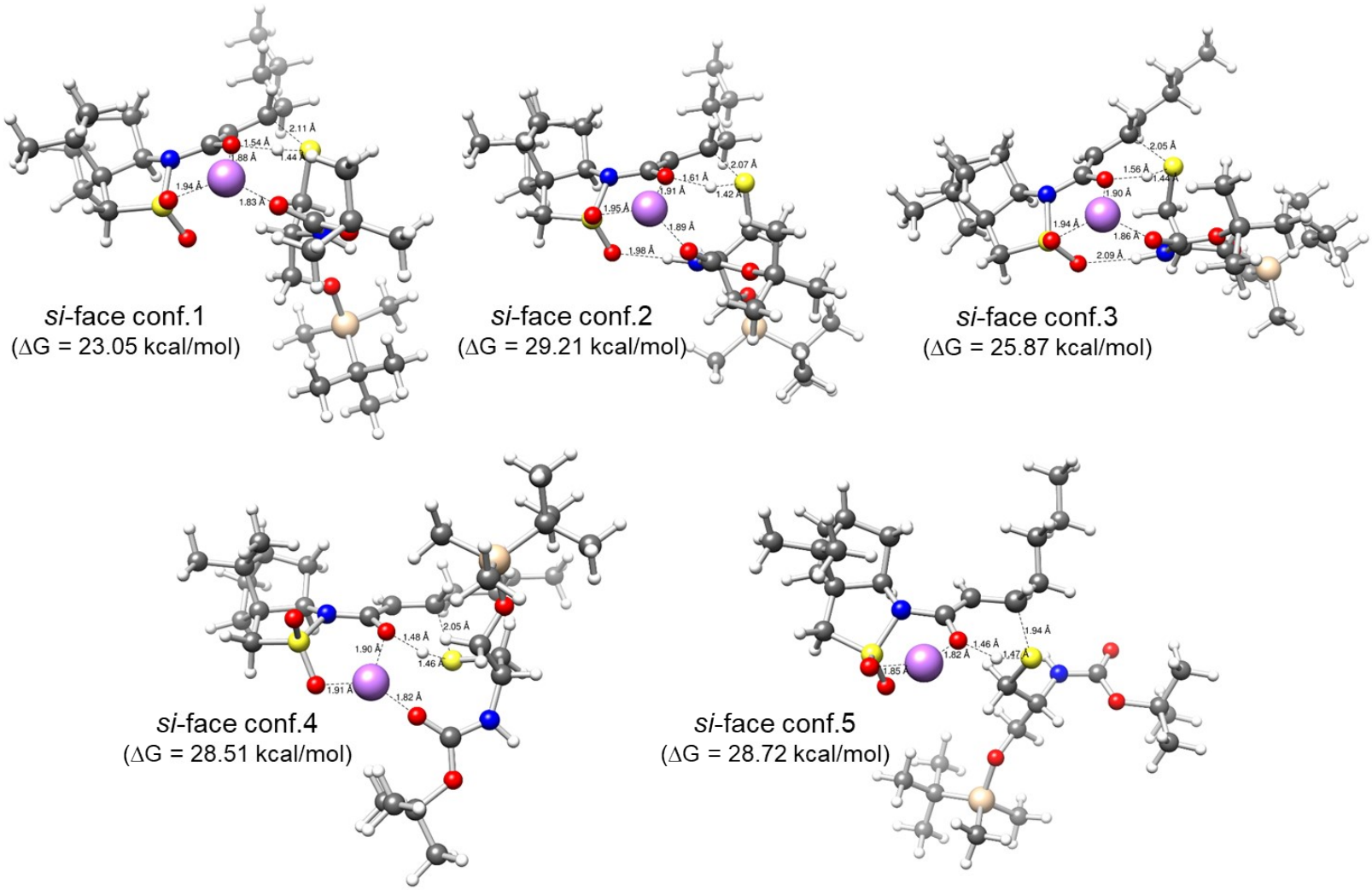


Figure S1. *Si*-face attack transition state geometries of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+. The relative free energies (ΔG) of each conformation to that of the lowest energy reactant complex are displayed in parentheses (Table S3). Polar hydrogens are displayed, and non-polar hydrogens are undisplayed for clarity. Color code: Si, tan; S, yellow; O, red; N, blue; C, gray; Li, magenta; H, white.

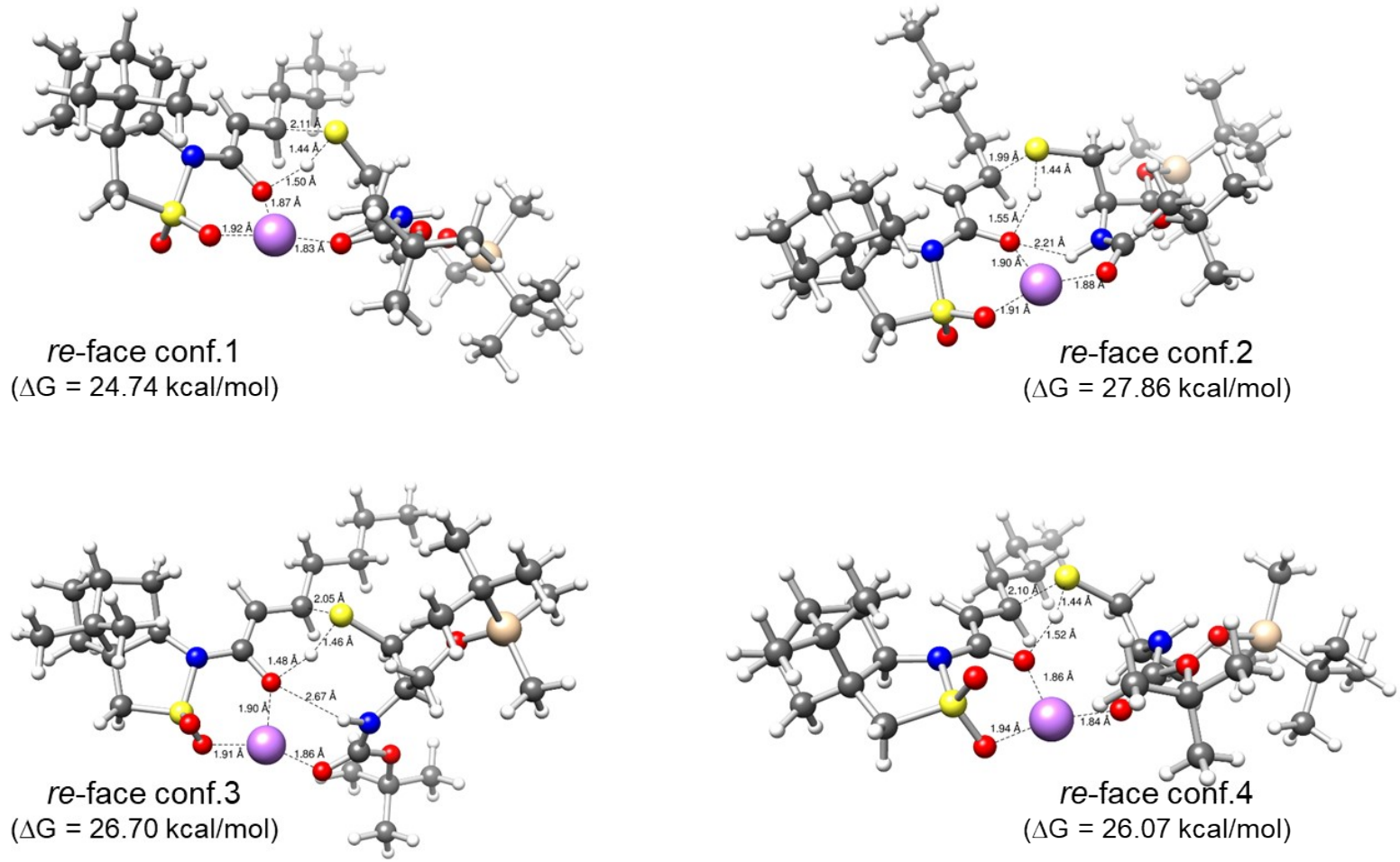


Figure S2. *Re*-face attack transition state geometries of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+. The relative free energies (ΔG) of each conformation to that of the lowest energy reactant complex are displayed in parentheses (Table S3). Polar hydrogens are displayed, and non-polar hydrogens are undisplayed for clarity. Color code: Si, tan; S, yellow; O, red; N, blue; C, gray; Li, magenta; H, white.

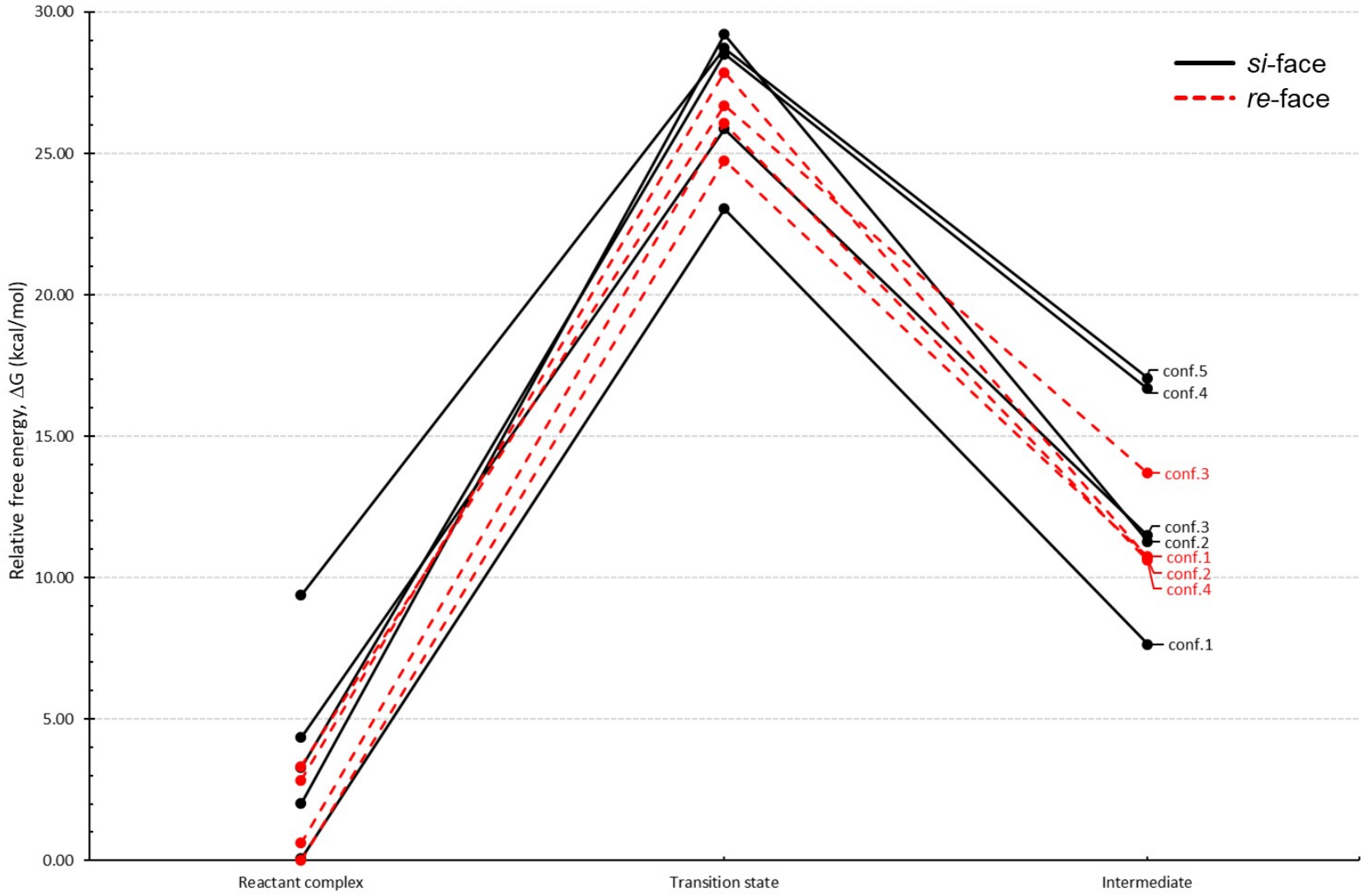


Figure S3. Relative free energy (ΔG) profiles of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+ calculated at M06(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level in dichloromethane. Data are displayed on Table S1.

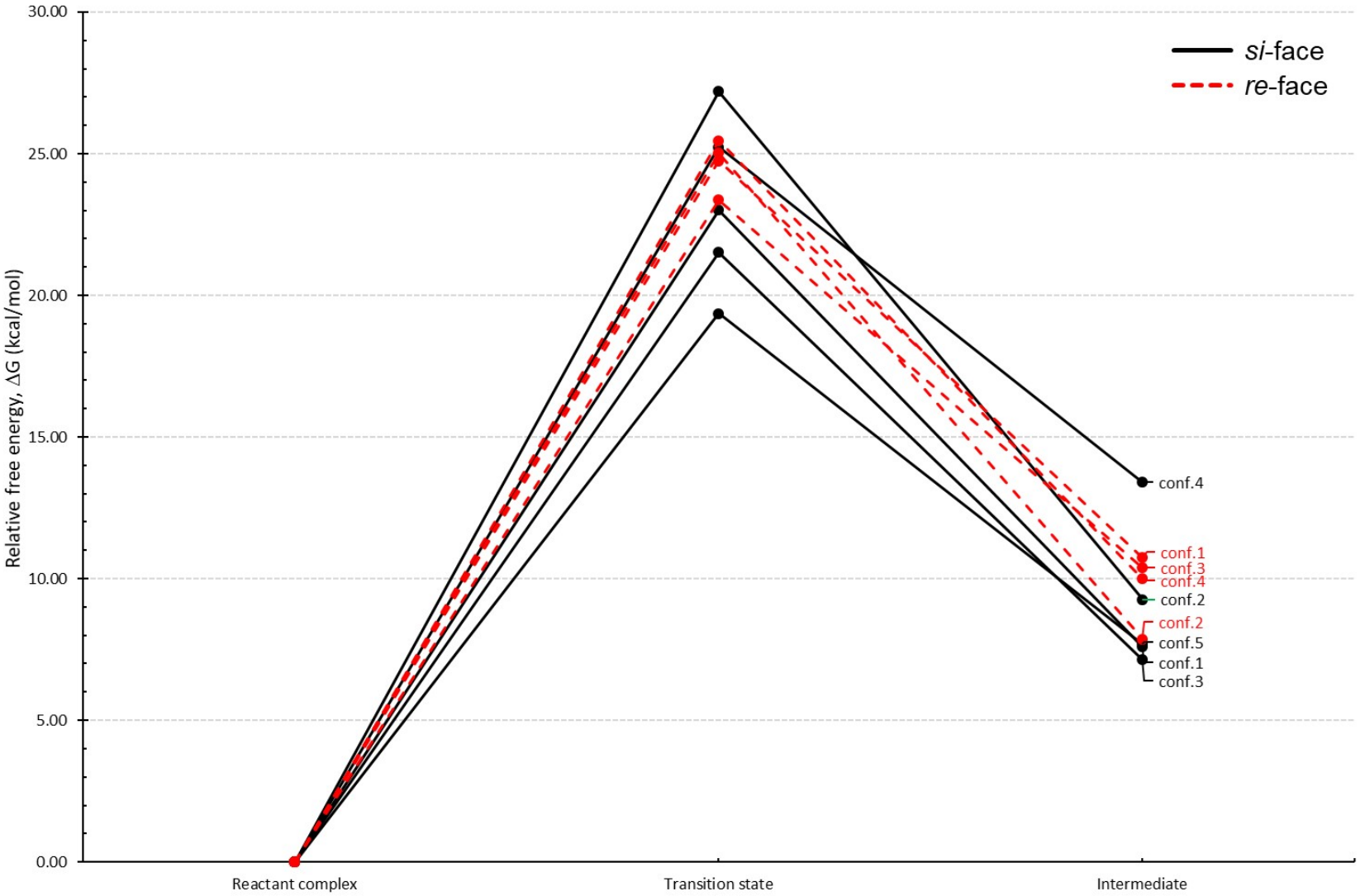


Figure S4. Relative free energy (ΔG) profiles of the sulfa-Michael addition step in thioamycolamide A synthesis with Li^+ calculated at M06(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level in dichloromethane. Relative energies of each reactant complex are adjusted to 0.00 kcal/mol. Data are displayed on Table S1.

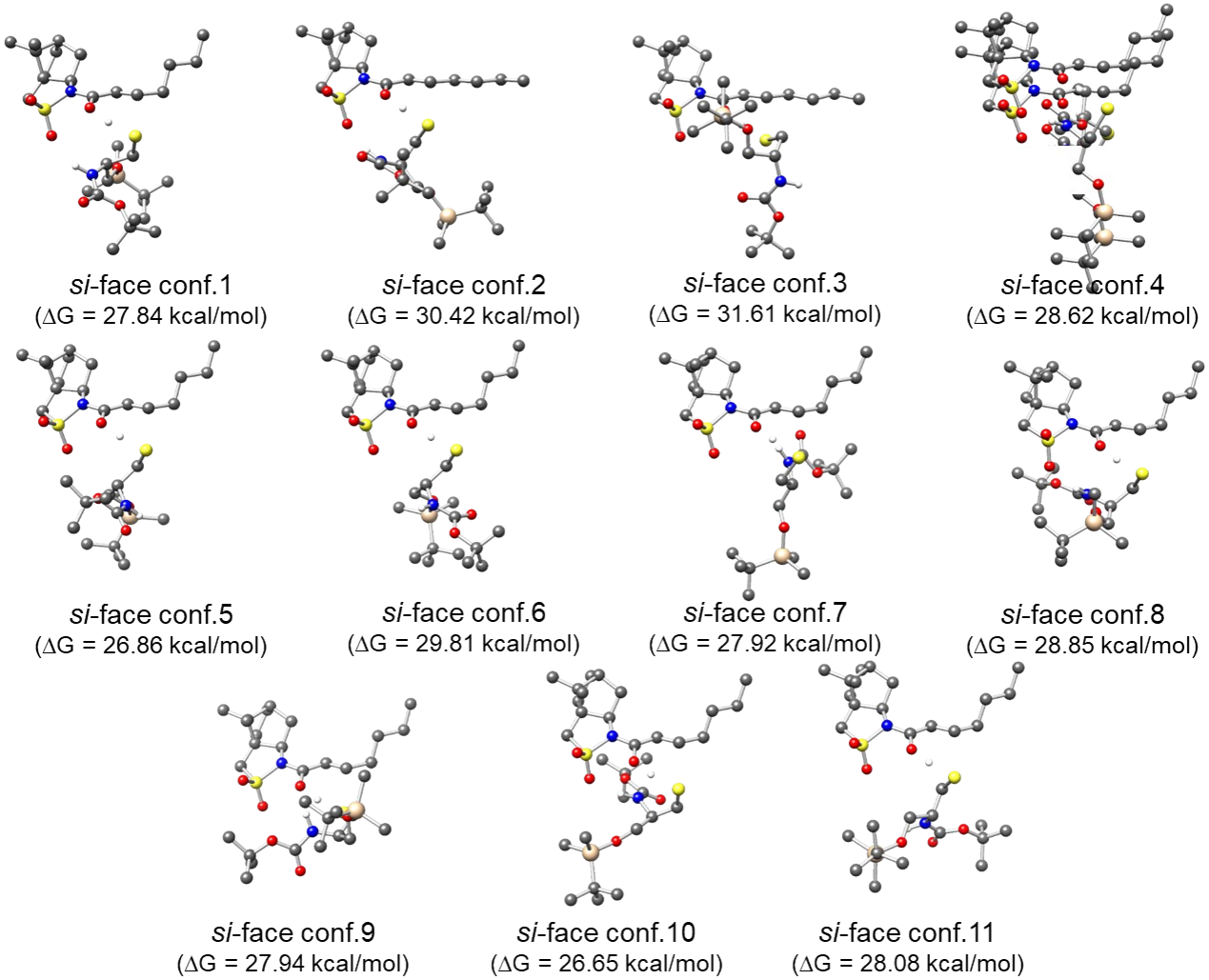


Figure S5. *Si*-face attack transition state geometries of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+. The relative free energies (ΔG) of each conformation to that of the lowest energy reactant complex are displayed in parentheses (Table S4). Polar hydrogens are displayed, and non-polar hydrogens are undisplayed for clarity. Color code: Si, tan; S, yellow; O, red; N, blue; C, gray; Li, magenta; H, white.

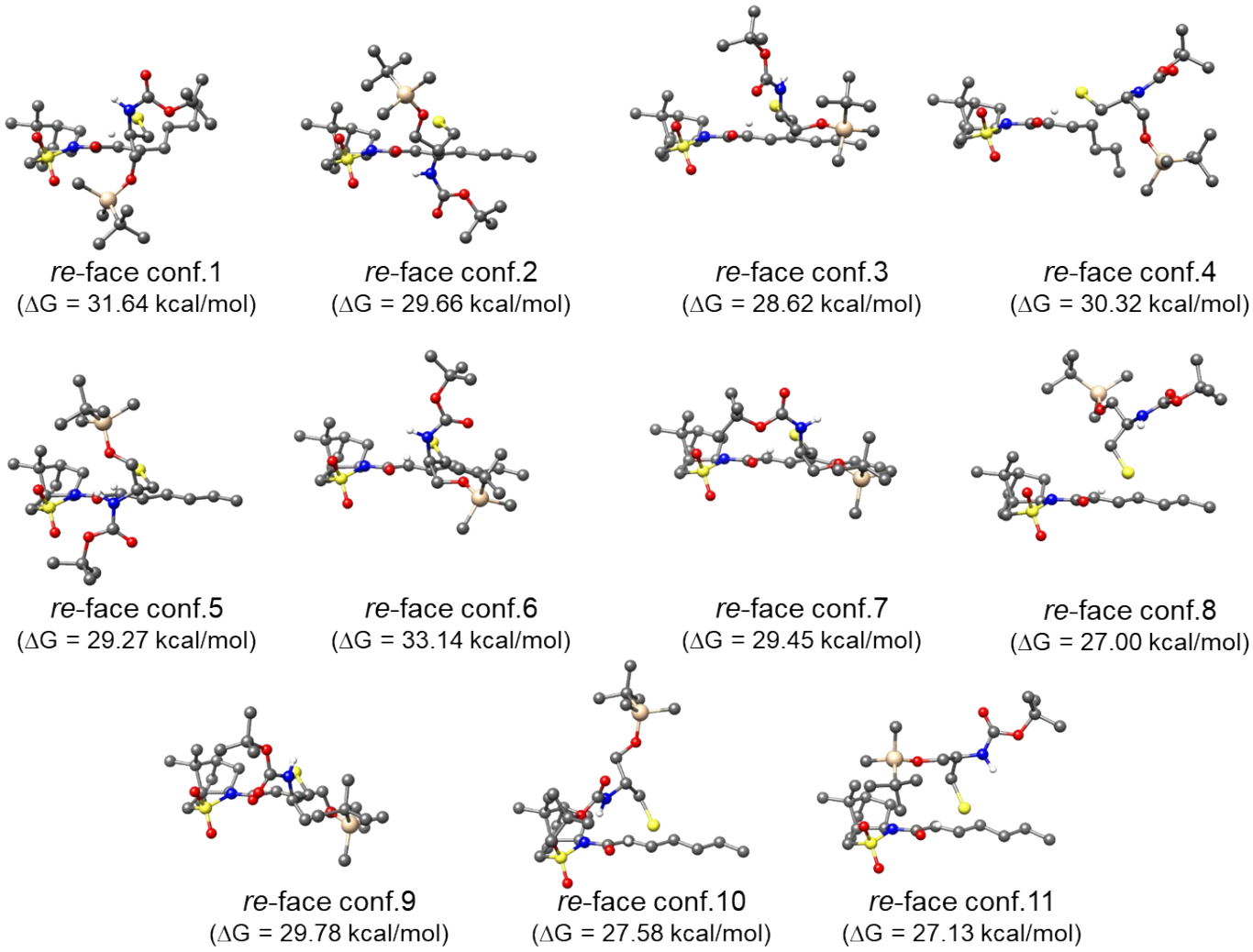


Figure S6. *Re*-face attack transition state geometries of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+. The relative free energies (ΔG) of each conformation to that of the lowest energy reactant complex are displayed in parentheses (Table S4). Polar hydrogens are displayed, and non-polar hydrogens are undisplayed for clarity. Color code: Si, tan; S, yellow; O, red; N, blue; C, gray; Li, magenta; H, white.

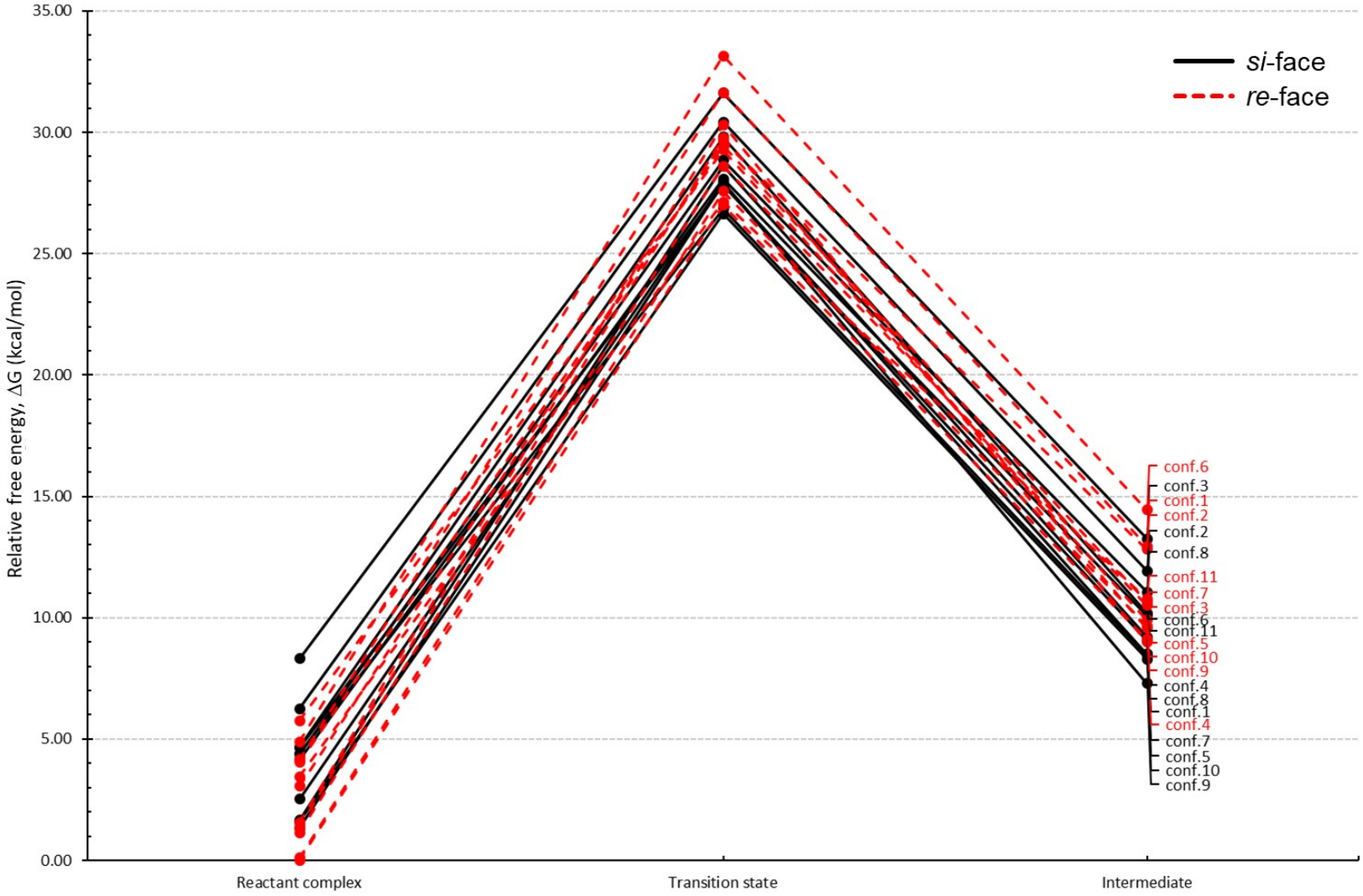


Figure S7. Relative free energy (ΔG) profiles of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+ calculated at M06(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level in dichloromethane. Data are displayed on Table S2.

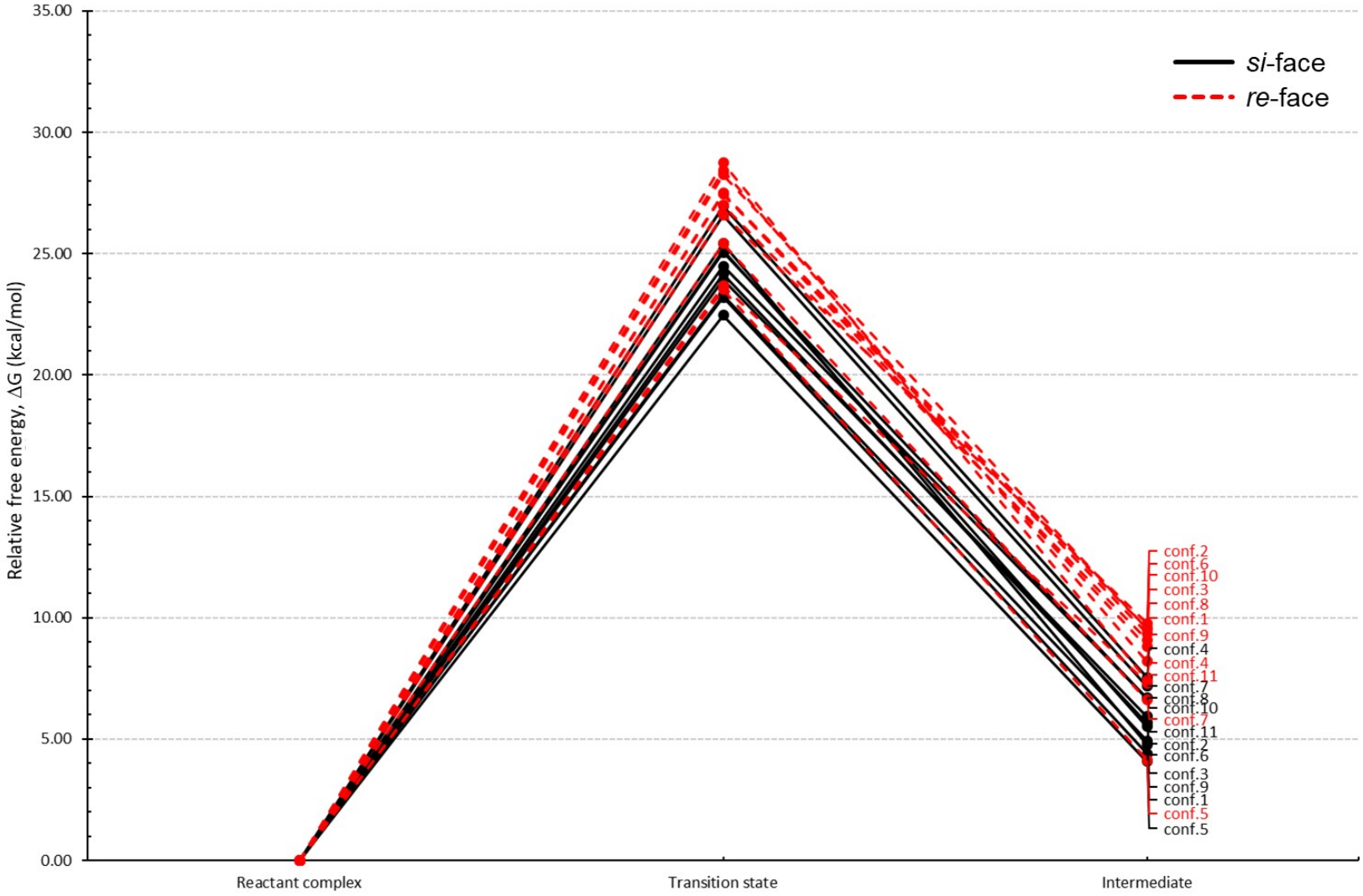


Figure S8. Relative free energy (ΔG) profiles of the sulfa-Michael addition step in thioamycolamide A synthesis without Li^+ calculated at M06(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level in dichloromethane. Relative energies of each reactant complex are adjusted to 0.00 kcal/mol. Data are displayed on Table S2.

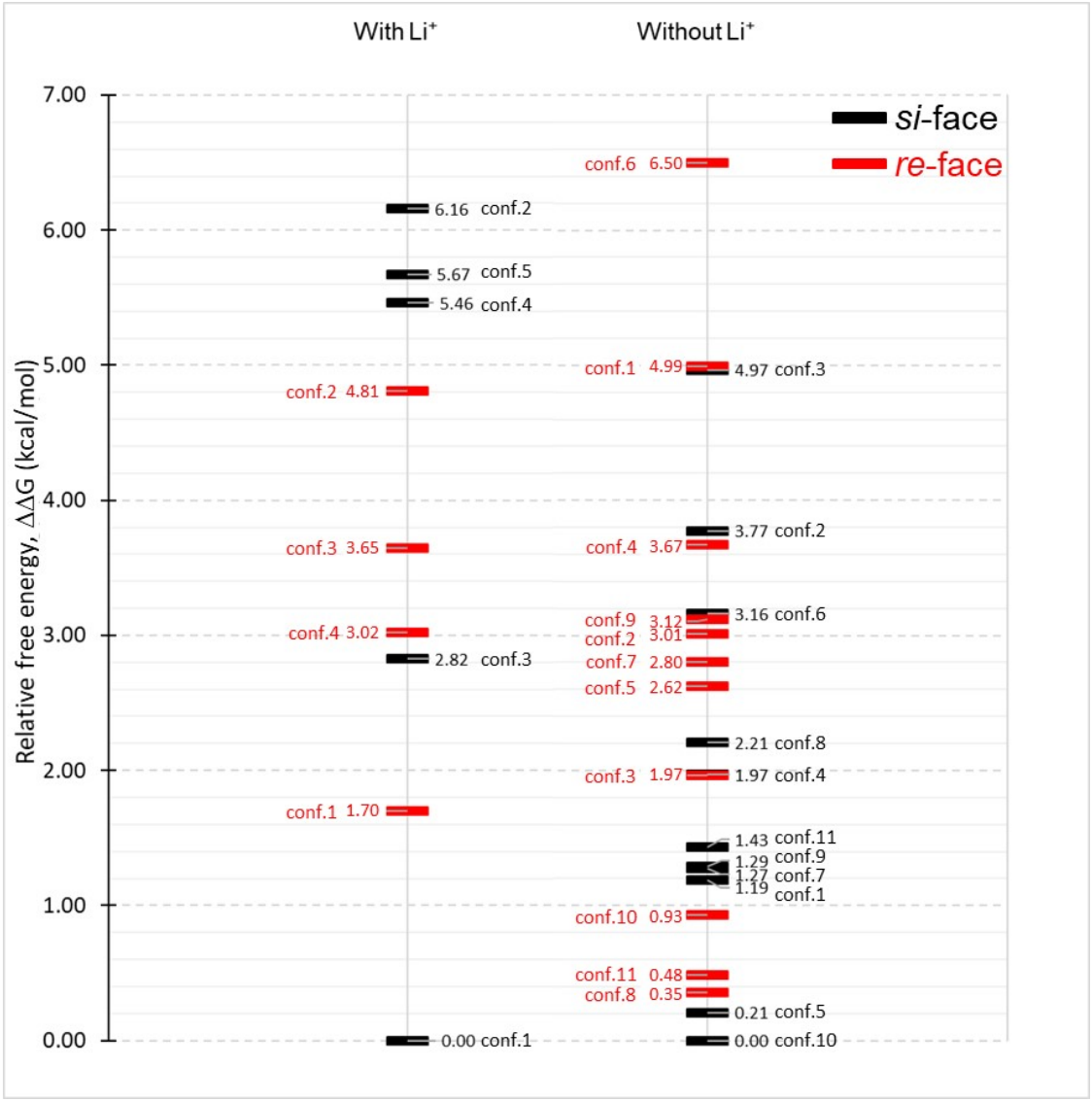


Figure S9. The free energies relative to the lowest energy transition state (ΔΔG) of the sulfa-Michael addition step in thioamycolamide A synthesis with and without Li^+ calculated at M06(SCRF)/6-311+G(d,p)//B3LYP/6-31+G(d,p) level. Data are displayed on Table S3 and S4.

VII. References

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